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L4 835299 S ADAPT###

L5 1 S L4(P)L3

=> s 12(5a)l1

L6 4 L2(5A)L1

=> d 1-4

1. 5,736,134, Apr. 7, 1998, Tissue plasminogen activator variants; Herbert L. Heyneker, et al., 424/94 64; 435/212, 252.3, 320.1, 325; 536/23.2 [IMAGE AVAILABLE]

2. 5,728,803, Mar. 17, 1998, Pantropic neurotrophic factors; Roman Urfert, et al., 530/350, 399 [IMAGE AVAILABLE]

3. 5,696,086, Dec. 9, 1997, Methods and kits using macrophage stimulating protein; Hava Karsenty Avraham, et al., 514/12; 530/351, 380 [IMAGE AVAILABLE]

4. 4,981,952, Jan. 1, 1991, Method for the purification of vitamin K-dependent proteins; S. Betty Yan, 530/384, 412, 413, 416, 417 [IMAGE AVAILABLE]
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(FILE 'USPAT' ENTERED AT 13:02:56 ON 20 JUL 1998)

L1 3300 S SERUM FREE

L2 18187 S 293

L3 74 S L1(P)L2

L4 835299 S ADAPT###

L5 1 S L4(P)L3

L6 4 S L2(5A)L1

=> s adeno or adenovirus

713 ADENO

2539 ADENOVIRUS

L7 2908 ADENO OR ADENOVIRUS

=> s 11(p)l7

L8 19 L1(P)L7

=> d 1-19

1. 5,773,289, Jun. 30, 1998, AAV directed targeted integration; Richard Jude Samulski, et al., 435/320.1, 69.1, 172.3, 325; 514/44; 800/2; 935/6, 23, 24, 32, 55, 57, 70 [IMAGE AVAILABLE]

2. 5,733,745, Mar. 31, 1998, Bovine heat shock promoter and uses thereof; Jacek Kowalski, et al., 435/69.3, 69.1, 172.3, 320.1, 325; 536/24.1 [IMAGE AVAILABLE]

3. 5,731,160, Mar. 24, 1998, Induction of antigen specific T-lymphocyte responses by stimulation with peptide loaded MHC class I molecules on antigen processing defective mammalian cell lines; Cornelis J. M. Melief, et al., 435/724; 424/93.71, 184.1, 534; 435/352, 355, 366, 375, 377; 436/501 [IMAGE AVAILABLE]

4. 5,726,290, Mar. 10, 1998, Soluble analogues of integrins; Sarah C. Bodary, et al., 530/350, 387.3 [IMAGE AVAILABLE]

5. 5,726,037, Mar. 10, 1998, Host cells and method of producing soluble analogues of integrins; Sarah C. Bodary, et al., 435/69.1, 69.7, 252.3, 325, 326 [IMAGE AVAILABLE]

6. 5,670,488, Sep. 23, 1997, Adenovirus vector for gene therapy; Richard J. Gregory, et al., 514/44; 424/93.2; 435/320.1; 935/62 [IMAGE AVAILABLE]

7. 5,660,986, Aug. 26, 1997, Immortalized human cell lines containing exogenous cytochrome P450 genes; Curtis C. Harris, et al., 435/6, 29, 32, 172.1 [IMAGE AVAILABLE]

8. 5,635,380, Jun. 3, 1997, Enhancement of nucleic acid transfer by coupling virus to nucleic acid via lipids; Allen J. Natflian, et al., 435/172.3; 424/85.2, 450; 435/172.1, 320.1 [IMAGE AVAILABLE]

9. 5,521,084, May 28, 1996, Bovine heat shock promoter and uses thereof; Jacek Kowalski, et al., 435/325, 320.1; 536/24.1 [IMAGE AVAILABLE]

10. 5,506,131, Apr. 9, 1996, Immortalized human cell lines containing exogenous cytochrome P450 genes; Curtis C. Harris, et al., 435/6, 371

[IMAGE AVAILABLE]

11. 5,443,954, Aug. 22, 1995, Immortalized non-tumorigenic human bronchial epithelial cell lines; Roger R. Reddel, et al., 435/7.21, 371 [IMAGE AVAILABLE]

12. 5,376,644, Dec. 27, 1994, Treatment of adenoviral infections with 3'-fluoro-5'-halo uracil compounds; John W. T. Selway, et al., 514/50, 49, 912; 536/28.2, 28.53, 28.55 [IMAGE AVAILABLE]

13. 5,356,806, Oct. 18, 1994, Immortalized human cell lines containing exogenous cytochrome P450; Curtis C. Harris, et al., 435/371, 69.1, 172.2 [IMAGE AVAILABLE]

14. 5,332,671, Jul. 26, 1994, Production of vascular endothelial cell growth factor and DNA encoding same; Napoleone Ferrara, et al., 435/360, 69.4, 69.6, 320.1; 536/23.5, 23.51 [IMAGE AVAILABLE]

15. 5,328,891, Jul. 12, 1994, Insulin-like growth factor binding protein and pharmaceutical compositions; Robert C. Baxter, et al., 514/2, 12; 530/350, 402 [IMAGE AVAILABLE]

16. 5,258,287, Nov. 2, 1993, DNA encoding and methods of production of insulin-like growth factor binding protein BP53; Robert C. Baxter, et al., 435/69.1, 6, 69.8, 252.3, 254.11, 254.2, 320.1, 365, 369; 536/23.5 [IMAGE AVAILABLE]

17. 5,070,078, Dec. 3, 1991, Antiviral compounds; John W. T. Selway, et al., 514/50; 424/408; 514/49; 536/28.2 [IMAGE AVAILABLE]

18. 5,037,743, Aug. 6, 1991, BARI secretion signal; Susan K. Welch, et al., 435/69.1, 172.3, 254.2, 320.1, 325; 536/23.2, 23.7, 24.1; 935/48, 60, 69, 70 [IMAGE AVAILABLE]

19. 4,885,238, Dec. 5, 1989, Immortalized human bronchial epithelial mesothelial cell lines; Roger R. Reddel, et al., 435/29, 6, 32, 172.1, 371, 948; 935/52, 57 [IMAGE AVAILABLE]

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3/7/19

DIALOG(R)File 357:Derwent Biotechnology Abs

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090645 DBA Accession No.: 89-08636

Harvesting and disruption of cells of recombinant *E. coli* in a continuous process for recombinant protein production, recovery and purification
- (conference abstract)

AUTHOR: Robinson C W; Flick B R; Sauer T; Wood D

CORPORATE SOURCE: Department of Biology, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

JOURNAL: Eur Congr Biotechnol. (Vol.2, 627) 1987

CODEN: 9999X

LANGUAGE: English

ABSTRACT: An integrated, multistage, continuous process for the production, recovery and purification of recombinant proteins was investigated. Biomass is produced in a 2-stage continuous loop fermentor, and following maximum gene expression, cells are continuously harvested by cross-flow microfiltration and subjected to disruption. The homogenizer effluent is then treated by either enzymatic (DNA-ase) or mechanical (ultrasonic) means in order to reduce viscosity and enhance the subsequent ultrafiltration step. The effects of microfiltration operating conditions (tangential shear rate, transmembrane pressure drop, cell concentration, membrane type, fermentation antifam) on the permeation flux and retentate cell concentration were examined for recombinant *Escherichia coli* cells producing phage T4 DNA-ligase. The effects of disruption conditions on percentage disruption and DNA-ligase release and the effect of viscosity reduction and other relevant ultrafiltration operating variables on the prefractionation recovery of active enzyme were also examined. Implications for recovery of other intracellular recombinant products were presented. (2 ref)

3/7/145

DIALOG(R)File 357:Derwent Biotechnology Abs

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046341 DBA Accession No.: 86-04189

The purification of alpha virus virions and subviral particles using ultrafiltration and gel exclusion chromatography - potential application to vaccine preparation

AUTHOR: Crooks A J; Lee J M; Stephenson J R

CORPORATE SOURCE: Vaccine Research and Production Laboratory, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire, UK.

JOURNAL: Anal Biochem. (152, 2, 295-303) 1986

CODEN: ANBCA2

LANGUAGE: English

ABSTRACT: The introduction of gel exclusion matrices suitable for very large molecules has enabled chromatographic purification of virus

particles. By combining gel exclusion chromatography with ultrafiltration, a technique for purifying enveloped viruses in a monodisperse native state has been developed. The process can be used for production of vaccines of defined immunogenic content. Sindbis virus (AR 339 isolate) was cultured in suspension cultures of primary avian fibroblasts. Cultures were centrifuged and the supernatants treated with sodium azide and aprotinin. They were concentrated and subjected to Sephacryl S400 column chromatography, and samples were examined by PAGE. Purified virus was incubated with Triton X-100 at 4 deg overnight prior to Sephacryl S400 column chromatography. Selected fractions were concentrated against an NM450 membrane, and fractions containing the envelope proteins were concentrated and dialyzed prior to S400 rechromatography. The method gave highly purified, intact alpha virus particles retaining high levels of biological activity, and was successfully used for viral envelope protein aggregate preparation. (14 ref)

3/7/166

DIALOG(R)File 357:Derwent Biotechnology Abs

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011033 DBA Accession No.: 83-02880

Concentration and analysis of labile viruses by hollow fibre ultrafiltration and ultracentrifugation - applied to rubella and human respiratory syncytial viruses

AUTHOR: Trudel M; Trepanier P; Payment P

CORPORATE SOURCE: Institut Armand-Frappier, Université du Québec, Centre de Recherche en Virologie, Laval-des-Rapides, Laval, Quebec, Canada H7N 4Z3.

JOURNAL: Process Biochem. (18, 1, 2-4, 9) 1983

CODEN: 7950W

LANGUAGE: English

ABSTRACT: Hollow fibre ultrafiltration proved a very successful method for the concentration of labile enveloped viruses. Rubella virus strain M-33 ATCC VR-315 was grown in Vero cells ATCC, CCL1, B1, which were produced in a tissue culture propagator. Viral supernatants showing haemagglutinating activity were collected and concentrated by hollow fibre ultrafiltration. This was carried out using alternatively the DC-10 and CH-4 systems in 4.5 hr. The combined recovery of 81.2% for a 2500 fold concentration. Only 12.1% of the protein content was found in the concentrate. Similarly 5 l of human respiratory syncytial virus suspension were concentrated using the Ch-4 system, with nearly 95% recovery of infectious units. The use of an Airfuge ultracentrifuge to separate viral cores allows the pelleting of rubella and human respiratory syncytial viruses in a short time. Rate zonal density centrifugation has also been applied to the screening of 125I labelled mouse monoclonal antibodies with specific binding affinity for the surface proteins. (14 ref)

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N2      72   34: SciSearch(R) Cited Ref Sci 1990-1998/Jul W4
N3      49   73: EMBASE_1974-1998/Aug W1
N4      46   15: MEDLINE(R)_1966-1998/Sep W4
N5      44   348: EUROPEAN PATENTS_1978-1998/Jul W3-
N6      40   5: BIOSIS PREVIEW(SR)_1969-1998/JUL W4
N7      31   636: IAC Newsletter DB(TM)_1987-1998/Aug 05
N8      27   144: Pascal_1973-1998/Jun
N9      17   442: AMA Journals_1982-1998/Jul W4
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N4      4   370: Science_1996-1998/Jun W3
N5      4   653: US Pat.Fulltext_1980-1989
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N7      1   148: IAC Trade & Industry Database_1976-1998/Aug 05
N8      1   158: DIOGENES(R)_1976-1998/Aug W1
N9      1  211: IAC Newsearch(TM)_1997-1998/Aug 05

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File 180: Federal Register 1985-1998/Aug 04

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File 370: Science 1996-1998/Jun W3

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File 653: US Pat.Fulltext 1980-1989

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*File 653: Reassignment data now current through 05/14/98.

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Reexamination, extension, expiration, reinstatement updated weekly.

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File 442: AMA Journals 1982-1998/Jul W4

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(c) 1998 Amer Med Assn -FARS/DARS apply

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File 148: IAC Trade & Industry Database 1976-1998/Aug 05

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File 158: DIOGENES(R) 1976-1998/Aug W1

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File 211: IAC Newsearch(TM) 1997-1998/Aug 05

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1/7/10 (Item 1 from file: 653)

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DIALOG(R)File 653: US Pat.Fulltext

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01795648

Utility

MOLECULARLY CLONED DIAGNOSTIC PRODUCT AND METHOD OF USE [MEMBRANE BOUND POLYPEPTIDE]

PATENT NO.: 4,855,224

ISSUED: August 08, 1989 (19890808)

INVENTOR(s): Berman, Philip W., San Francisco, CA (California), US (United States of America)

Lasky, Laurence A., San Francisco, CA (California), US (United States of America)

ASSIGNEE(s): Genentech, Inc., (A U.S. Company or Corporation), South San Francisco, CA (California), US (United States of America)

[Assignee Code(s): 7579]

APPL. NO.: 6-776,059

FILED: September 13, 1985 (19850913)

This application is a continuation of application Ser. No. 587,763, filed Mar. 9, 1984, now abandoned.

This is a continuation-in-part of application Ser. No. 527,916, filed Aug. 30, 1983, now abandoned, and of application Ser. No. 547,552 filed Oct. 31, 1983, now abandoned.

FULL TEXT: 1716 lines

ABSTRACT

A molecularly cloned diagnostic product in the form of a polypeptide with antigenic determinants capable of specifically binding complementary antibody, the polypeptide being expressed from a stable continuous cell line. With a glycoprotein D of Herpes Simplex Virus (HSV) as the polypeptide, HSV antibody in a specimen is detected in an immunological procedure. With a glycoprotein C fragment from HSV type 2, HSV type 2 may be distinguished from HSV type 1.

What is claimed is:

1. A diagnostic product comprising membrane-bound polypeptide having antigenic determinants capable of specifically binding complementary antibody to herpes simplex virus, said polypeptide being functionally associated with the membrane of a recombinant, stable, continuous cell line capable of its production.
2. The diagnostic product of claim 1 in which said polypeptide is a glycoprotein D of herpes simplex virus type 1 or type 2, and is capable of binding antibodies of herpes simplex virus type 1 and/or type 2.
3. The diagnostic product of claim 1 in which said polypeptide is a glycoprotein C of herpes simplex virus type 1 or type 2.
4. The diagnostic product of claim 3 in which said polypeptide comprises a fragment of glycoprotein C of herpes simplex virus type 2 and is capable of binding complementary antibodies to herpes simplex virus type 1 or type 2.
5. The diagnostic product of claim 3 in which the polypeptide comprises a

fragment of glycoprotein C capable of binding complementary antibodies to herpes simplex virus type 2, but not herpes simplex virus type 1.

6. The diagnostic product of claim 1 bound to a solid surface.

7. The diagnostic product of claim 1 linked to a label.

8. The diagnostic product of claim 7 in which said label comprises an enzyme.

9. The diagnostic product of claim 1 in which said recombinant cell is mammalian.

10. The diagnostic product of any one of claims 1, 2 to 8, or 9 in a diagnostic test kit, together with a labeled anti-antibody capable of specifically binding said complementary antibody.

11. The diagnostic product of claim 10 together with unlabeled complementary antibody in said diagnostic test kit.

12. The diagnostic product of any one of claims 1, 2 to 7 or 8, together with labeled complementary antibody in a diagnostic test kit.

13. A diagnostic test kit comprising:

(a) a diagnostic product comprising a membrane-bound polypeptide with antigenic determinants capable of specifically binding complementary antibodies to herpes simplex virus, said polypeptide being formed in a recombinant, stable, continuous cell line; and

(b) a second component comprising either said complementary antibody or anti-antibody capable of specifically binding said complementary antibody.

14. The diagnostic test kit of claim 13 in which said diagnostic product is bound to a solid surface.

15. The diagnostic test kit of claim 13 in which said diagnostic product is linked to a label.

16. The diagnostic test kit of claim 13 in which said second component comprises labeled anti-antibody capable of specifically binding said complementary antibody.

17. The diagnostic test kit of claim 16 further comprising unlabeled complementary antibody.

18. The diagnostic test kit of claim 13 in which said second component comprises complementary antibody.

19. The diagnostic test kit of claim 13 in which said diagnostic product is a truncated, membrane-free derivative of a polypeptide, said derivative being devoid of a membrane-binding domain whereby the derivative is free of said membrane.

20. The diagnostic test kit of claim 19 in which the truncated polypeptide is formed by secretion from a recombinant eukaryotic host cell system capable of its production.

21. The diagnostic test kit of claim 13 in which the diagnostic product comprises a membrane-free derivative of the polypeptide in which the polypeptide first is formed functionally associated with a membrane of said recombinant, stable, continuous cell line and then dissolved free from said membrane.

22. The diagnostic test kit of claim 13 in which said diagnostic product comprises a glycoprotein of herpes simplex virus type 1 or type 2.

23. The diagnostic test kit of claim 22 in which said glycoprotein is capable of binding either herpes simplex virus type 1 or type 2, but not both.
24. The diagnostic test kit of claim 22 in which said glycoprotein is capable of binding complementary antibodies to either herpes simplex virus type 1 or type 2, but not both.
25. The diagnostic test kit of claim 22 in which said diagnostic product comprises a glycoprotein C of herpes simplex virus type 1 or type 2.
26. The diagnostic test kit of claim 25 in which said glycoprotein C is of herpes simplex virus type 2.
27. The diagnostic test kit of claim 26 in which said polypeptide comprises a fragment of herpes simplex virus type 2 capable of binding complementary antibodies to herpes simplex type 2, but not herpes simplex type 1.
28. A method for the detection of antibody contained in a biologically derived fluid sample comprising the steps of:
- (a) contacting said fluid sample with the diagnostic product of claim 1 to bind the diagnostic product with complementary antibody in the fluid sample; and
- (b) detecting the binding of step (a).
29. The method of claim 28 in which the binding of step (a) is also measured.
30. The method of claim 28 in which in step (a) said diagnostic reagent is bound to a solid surface, and said sample also is contacted with soluble labeled anti-antibody capable of specifically binding said complementary antibody, to cause said sample antibody to bond on said solid surface both to said diagnostic product and said labeled anti-antibody; said method further comprising prior to step (b) separating the solid surface from the solution containing unreacted, soluble labeled antibody; and wherein in step (b) the labeled anti-antibody is detected in either the solid phase or the separated solution.
31. The method of claim 29 in which in step (a) said diagnostic product is bound to a solid surface, and said sample also is contacted with soluble labeled antibody also capable of specifically binding said diagnostic product, to cause said sample antibody and labeled antibody to bind competitively to said diagnostic product on said solid surface; said method further comprising prior to step (b) separating the solid surface from the solution containing unreacted, soluble labeled antibody, and wherein in step (b) the labeled antibody is detected in either the solid phase or the separated solution.
32. A method for the detection of antigen contained in a biologically derived fluid sample, comprising the steps of:
- (a) contacting said fluid sample with a diagnostic product of claim 1; said diagnostic product having the same antigenic determinants as said sample antigen; and
- (b) detecting the sample antigen using a competitive assay.
33. The method of claim 32 in which in step (a) said diagnostic product

is bound to a solid surface, and said sample also is contacted with soluble unlabeled complementary antibody, to cause competition binding for said complementary antibody between said diagnostic product and sample antigen, said method further comprising, prior to step (b), the steps of:

(c) separating the solid surface from the solution; and

(d) contacting the separated solid surface or solution with labeled anti-antibody capable of specifically binding said complementary antibody, and wherein in step (b) the labeled anti-antibody is detected.

34. The method of claim 32 in which said diagnostic product is labeled and in step (a) said sample is also contacted with immobilized complementary antibody to set up a competitive binding between the labeled diagnostic product and the sample antigen.

1/7/11 (Item 2 from file: 653)

DIALOG(R)File 653:US Pat.Fulltext

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01793598

Utility

HUMAN TISSUE PLASMINOGEN ACTIVATOR

PATENT NO.: 4,853,330

ISSUED: August 01, 1989 (19890801)

INVENTOR(s): Goeddel, David V., Hillsborough, CA (California), US (United

States of America)

Kohr, William J., San Mateo, CA (California), US (United

States of America)

Pennica, Diane, Foster City, CA (California), US (United

States of America)

Vehar, Gordon A., San Carlos, CA (California), US (United

States of America)

ASSIGNEE(s): Genentech, Inc., (A U.S. Company or Corporation), South San

Francisco, CA (California), US (United States of America)

[Assignee Code(s): 7579]

APPL. NO.: 7-184,477

FILED: April 21, 1988 (19880421)

DISCLAIMER: August 23, 2005 (20050823)

This application is a continuation application of application Ser. No.

483,052, filed Apr. 7, 1983, now U.S. Pat. No. 4,766,075, which is a

continuation-in-part of applications Ser. No. 398,003 filed July 14, 1982

and Ser. No. 374,860, filed May 5, 1982, both now abandoned.

FULL TEXT: 2034 lines

ABSTRACT

Human tissue plasminogen activator (t-PA) is produced in useful quantities using recombinant DNA techniques. The invention disclosed thus enables the production of t-PA free of contaminants with which it is ordinarily associated in its native cellular environment. Methods, expression vehicles and various host cells useful in its production are also disclosed.

We claim:

1. A process which comprises expressing a DNA sequence encoding human tissue plasminogen activator in a recombinant host cell, said recombinant host cell being a microorganism or cell culture transformed with an expression vector containing said DNA sequence.
2. A process according to claim 1 which additionally comprises the step of recovering said human tissue plasminogen activator.
3. A process according to claim 2 wherein the host cell is of a mammalian cell line.
4. A process according to claim 3 wherein the cell line is a Chinese hamster ovary cell line.
5. The process according to claim 1 wherein said microorganism is *E. coli*.
6. A process according to claim 1 wherein said human tissue plasminogen activator has the amino acid sequence 1-527 set forth in FIGS. 5a, 5b and 5c.
7. A process to claim 4 wherein said human tissue plasminogen activator has the amino acid sequence 1-527 set forth in FIGS. 5a, 5b and 5c.
8. A process for producing recombinant human tissue plasminogen activator comprising:
 - (a) growing recombinant cells in a growth medium, said cells being a microorganism or cell culture transformed with an expression vector containing DNA encoding human tissue plasminogen activator; and
 - (b) simultaneously expressing said DNA, thereby producing recombinant human tissue plasminogen activator.
9. The process of claim 8, wherein said DNA codes for the amino acid sequence 1-527 of FIGS. 5a, 5b, and 5c hereof.
10. The process of claim 8, wherein said microorganism is *E. coli*.
11. The process of claim 8, wherein said cells are Chinese hamster ovary cells.
12. A process for producing recombinant human tissue plasminogen activator comprising:
 - (a) transforming a microorganism or cell culture with a replicable vector containing DNA encoding human tissue plasminogen activator; and
 - (b) expressing said DNA in said transformed microorganism or cell culture.
13. The process of claim 12, wherein said DNA codes for the amino acid sequence 1-527 of FIGS. 5a, 5b, and 5c hereof.
14. The process according to claim 12 wherein said microorganism is *E. coli*.
15. The process according to claim 12 wherein said cell culture is a Chinese hamster ovary cell line.

1/7/12 (Item 3 from file: 653)
 DIALOG(R)File 653:US Pat.Fulltext
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 01700114
 Utility

HUMAN TISSUE PLASMINOGEN ACTIVATOR

[FROM CELL CULTURES USING RECOMBITANT DNA]

PATENT NO.: 4,766,075

ISSUED: August 23, 1988 (19880823)

INVENTOR(s): Goeddel, David V., Hillsborough, CA (California), US (United States of America)

Kohr, William J., San Mateo, CA (California), US (United States of America)

Pennica, Diane, Foster City, CA (California), US (United States of America)

Vebar, Gordon A., San Carlos, CA (California), US (United States of America)

ASSIGNEE(s): Genentech, Inc., (A U.S. Company or Corporation), South San Francisco, CA (California), US (United States of America)

[Assignee Code(s): 7579]

APPL. NO.: 6-483,052

FILED: April 07, 1983 (19830407)

This is a continuation-in-part of applications Ser. No. 398,003 filed July 14, 1982 and Ser. No. 374,860, filed May 5, 1982.

FULL TEXT: 1645 lines

ABSTRACT

Human tissue plasminogen activator (t-PA) is produced in useful quantities using recombinant DNA techniques. The invention disclosed thus enables the production of t-PA free of contaminants with which it is ordinarily associated in its native cellular environment. Methods, expression vehicles and various host cells useful in its production are also disclosed.

We claim:

1. A DNA isolate consisting essentially of a DNA sequence encoding human tissue plasminogen activator.
2. The DNA isolate of claim 1 wherein said human tissue plasminogen activator has the amino acid sequence 1-527 set forth in FIGS. 5a, 5b and 5c.
3. A recombinant expression vector containing a DNA sequence encoding human tissue plasminogen activator, wherein the vector is capable of expressing human tissue plasminogen activator in a transformed microorganism or cell culture.
4. The recombinant expression vector of claim 3 wherein said human tissue plasminogen activator has the amino acid sequence 1-527 set forth in FIGS. 5a, 5b and 5c.
5. A microorganism transformed with the vector of claim 3, said microorganism being capable of expressing human tissue plasminogen activator.
6. An *E. coli* microorganism according to claim 5.
7. The microorganism of claim 5 wherein said human tissue plasminogen activator has the amino acid sequence 1-527 set forth in FIGS. 5a, 5b and 5c.

8. A cell culture capable of expressing human tissue plasminogen activator, obtained by transforming a mammalian cell line with a vector according to claim 3.
9. A cell culture according to claim 8 wherein the cell line is a Chinese Hamster Ovary cell line.
10. The cell culture of claim 8 wherein said human tissue plasminogen activator has the amino acid sequence 1-527 set forth in FIGS. 5a, 5b and 5c.
11. The cell culture of claim 9 wherein said human tissue plasminogen activator has the amino acid sequence 1-527 of FIGS. 5a, 5b and 5c.

1/7/13 (Item 4 from file: 653)

DIALOG(R) File 653: US Pat. Fulltext

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01683994

Utility

METHODS AND COMPOSITIONS USEFUL IN THE DIAGNOSIS AND TREATMENT OF AUTOIMMUNE DISEASES [GENETIC ENGINEERING]

PATENT NO.: 4,751,181

ISSUED: June 14, 1988 (19880614)

INVENTOR(s): Keene, Jack D., Durham, NC (North Carolina), US (United States of America)

ASSIGNEE(s): Duke University, (A U.S. Company or Corporation), Durham, NC (North Carolina), US (United States of America)

[Assignee Code(s): 25202]

APPL. NO.: 6-687,908

FILED: December 31, 1984 (19841231)

The investigations leading to the present invention were supported in part by a grant from the National Institutes of Health.

FULL TEXT: 1049 lines

ABSTRACT

A method for producing a protein antigen which is reactive with an autoantibody associated with an autoimmune disease in a host, which comprises introducing genetic information from a cross-reactive donor gene library, into plural cells thereby producing transformed cells; selecting a producer cell which expresses said antigen by detecting a binding reaction between said autoantibody obtained from said host and a protein antigen expressed by a producer cell of said transformed cells which contains a gene coding for said protein antigen, thereby identifying a cloned DNA segment from said donor which can be utilized in the production of said protein, is disclosed along with biochemical reagents and products associated with this invention.

What is new and desired to be secured by Letters Patent of the United States is:

1. A method for producing a La protein antigen which is reactive with an autoantibody associated with systemic lupus erythematosus in a host, which comprises:
 - introducing genetic information from a gene library obtained from a first host into plural recipient cells, wherein said gene library is obtained from a host that expresses a La protein antigen reactive with said autoantibody, thereby producing transformed cells;
 - selecting a producer cell from said transformed cells which contains a gene coding for said La protein antigen and which expresses said antigen by detecting a binding reaction between an autoantibody obtained from a second and different host and protein antigen expressed by said producer cell, thereby identifying a cloned DNA segment which can be utilized in the production of said protein antigen.

2. A method for producing a La protein antigen which is reactive with an autoantibody associated with systemic lupus erythematosus in a host, which comprises:

introducing genetic information from a gene library obtained from a first host into plural recipient cells, wherein said gene library is obtained from a host that expresses a La protein antigen reactive with said autoantibody, thereby producing transformed cells;

selecting a producer cell from said transformed cells which contains a gene coding for said La protein antigen and which expresses said antigen by detecting a binding reaction between an autoantibody obtained from a second and different host and protein antigen expressed by said producer cell, thereby identifying a cloned DNA segment which can be utilized in the production of said protein;

cloning said producer cells; and

obtaining said La protein antigen expressed by said producer cell.

3. A method for producing a La protein antigen which is a reactive with an autoantibody associated with systemic lupus erythematosus in a host, which comprises:

introducing genetic information from a gene library obtained from a first host into plural recipient cells, wherein said gene library is obtained from a host that expresses a La protein antigen reactive with said autoantibody, thereby producing transformed cells;

selecting a producer cell from said transformed cells which contains a gene coding for said La protein antigen and which expresses said antigen by detecting a binding reaction between an autoantibody obtained from a second and different host and the protein antigen expressed by said producer cell, thereby identifying a cloned DNA segment which can be utilized in the production of said protein;

sequencing said gene or said La protein antigen; and synthesizing said La protein by chemical means.

4. The method of claim 1, wherein said first host is a human.

5. The method of claim 1, wherein said second and different host is a human.

6. The method of claim 2, wherein said first host is a human.

7. The method of claim 2, wherein said second and different host is a human.
8. The method of claim 1, wherein said donor gene library is a cDNA gene library.
9. The method of claim 2, wherein said donor gene library is a cDNA gene library.
10. A recombinant DNA expression vector, wherein said vector comprises an expressible DNA segment which codes for a La protein antigen which is reactive with an autoantibody associated with systemic lupus erythematosus.
11. The vector of claim 10, wherein said segment codes for at least 66 amino acids at the carboxy terminal of a human La protein antigen.
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SYSTEM OS - DIALOG OneSearch

File 155:MEDLINE(R) 1966-1998/Sep W4
(c) format only 1998 Dialog Corporation
File 73:EMBASE 1974-1998/Aug W1
(c) 1998 Elsevier Science B.V.

Set Items Description

27237 ADENOVIR?
2725 ADENO
596020 VIRUS?
75 ADENO(W)VIRUS?
201863 PERFUS?
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S2 61 RD (unique items)
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? sf allscience
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(To see banners, use SHOW FILES command)
? s (adeno(w)virus? or adenovir?) and scale?
? rf
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S (ADENO(W)VIRUS? OR ADENOVIR?) AND SCALE?
Ref Items File

N1 1035 654: US Pat Full_1990-1998/Jul 28
N2 382 348: EUROPEAN PATENTS_1978-1998/Jul W3-
N3 69 653: US Pat Fulltext_1980-1989

N4 45 636: IAC Newsletter DB(TM)_1987-1998/Aug 05
 N5 37 34: SciSearch(R) Cited Ref Sci_1990-1998/Jul W4
 N6 34 442: AMA Journals_1982-1998/Jul W4
 N7 32 73: EMBASE_1974-1998/Aug W1
 N8 30 148: IAC Trade & Industry Database_1976-1998/Aug 05
 N9 28 180: Federal Register_1985-1998/Aug 04
 N10 27 5: BIOSIS PREVIEW(SR)_1969-1998/JUL W4
 N11 26 155: MEDLINE(R)_1966-1998/Sep W4
 N12 25 16: IAC PROMT(R)_1972-1998/Aug 05
 N13 20 76: Life Sciences Collection_1982-1998/Jun
 N14 18 50: CAB Abstracts_1972-1998/Jun
 N15 15 370: Science_1996-1998/Jun W3
 N16 12 351: DERWENT WPI_1963-1998/UD=9830;UP=9827;UM=9825
 N17 11 266: FEDRIP_1998/Jun
 N18 11 652: US Patents Fulltext_1971-1979
 N19 10 434: SciSearch(R) Cited Ref Sci_1974-1989/Dec
 N20 9 444: New England Journal of Med_1985-1998/Aug W1
 N21 9 457: The Lancet_1986-1998/Jul W4
 N22 8 621: IAC New Prod. Annou.(R)_1985-1998/Aug 05
 N23 7 9: Business & Industry(R) Jul_1994-1998/Aug 05
 N24 7 144: Pascal_1973-1998/Jun
 N25 7 649: IAC NEWSWIRE ASAP(TM)_1998/Aug 05
 N26 6 6: NTIS_64-1998/Aug W5
 N27 5 15: ABI/INFORM(R)_1971-1998/Jul W4
 N28 4 35: Dissertation Abstracts Online_1861-1998/Aug
 N29 4 187: F-D-C Reports_1987-1998/Jul W4
 N30 4 211: IAC Newsearch(TM)_1997-1998/Aug 05
 N31 4 315: ChemEng & Biotec Abs_1970-1998/Aug
 N32 4 624: McGraw-Hill Publications_1985-1998/Aug 04
 N33 4 764: BCC Market Research_1989-1998/Jun
 N34 4 765: Frost & Sullivan_1992-1998/Jul
 N35 3 20: World Reporter_1997-1998/Aug 05
 N36 3 388: PEDS: Defense Program Summaries_1998/Jun
 N37 3 660: Federal News Service_1991-1998/Aug 04
 N38 2 8: Ei Compendex(R)_1970-1998/Aug W4
 N39 2 51: Food Sci.&Tech.Abs_1969-1998/Jul
 N40 2 65: Inside Conferences_1993-1998/Aug W1
 N41 2 98: General Sci Abs/Full-Text_1984-1998/Jun
 N42 2 156: Toxline(R)_1965-1998/Jul
 N43 2 158: DIOGENES(R)_1976-1998/Aug W1
 N44 1 43: Health News Daily_1990-1998/Aug 04
 N45 1 77: Conference Papers Index_1973-1998/Jul
 N46 1 94: JICST-EPlus_1985-1998/May W4
 N47 1 103: Energy SciTec_1974-1998/Jul B1
 N48 1 108: Aerospace Database_1962-1998/July
 N49 1 172: EMBASE Alert_1998/Aug W2
 N50 1 376: Derwent Drug File_1964-1982

N51 1 635: Business Dateline(R)_1985-1998/Jul W4
 51 files have one or more items; file list includes 145 files.
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 File 315:ChemEng & Biotec Abs 1970-1998/Aug
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 13810 SCALE?
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 DIALOG(R)File 315:ChemEng & Biotec Abs
 (c)1998 RoySocChm,DECHEMA,FizChemie. All rts. reserv.
 385514 CEABA Accession No.: 27-05-009938 DOCUMENT TYPE: Patent
 Title: Methods and compositions for the large-scale production of
 recombinant adeno-associated virus.
 AUTHOR: Dong, Jianyun ; Frizzell, R. A.
 CORPORATE SOURCE: UAB Res. Foundation Birmingham, AL 35294-2010 USA
 CODEN: PLXXD2
 PATENT NUMBER: WO 9506743
 PUBLICATION DATE: 9 Mar 1995 (950309) LANGUAGE: English
 PRIORITY PATENT APPLICATION(S) & DATE(S): US 8114595 (930831)
 ABSTRACT: Novel methods and compositions are disclosed for use in the
 efficient and large-scale production of recombinant adeno-associated
 virus. New producer cell lines, recombinant adenovirus or herpes virus
 vectors and AVV constructs are provided. The vectors are of use for
 transferring exogenous genes into human cell lines and for human gene
 therapy.
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File 351:DERWENT WPI 1963-1998/UD=9830;UP=9827;UM=9825

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*File 351: All images are now present. The display formats have changed for 1998. See HELP FORM 351 for more information.

Set Items Description

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258 ADENO

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36 ADENOV(W)VIRUS?

636 ADENOVIR?

80217 SCALE?

S1 12 (ADENO(W)VIRUS? OR ADENOVIR?) AND SCALE?

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DIALOG(R)File 351:DERWENT WPI

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011931601

WPI Acc No: 98-348511/199830

XRAM Acc No: C98-107812

Purification of, e.g. recombinant adenovirus from aqueous preparation - by anion-exchange chromatography then size exclusion chromatography, useful to, e.g. produce purified viruses for gene therapy and vaccines

Patent Assignee: SCHERING CORP (SCHE)

Inventor: BONDOL L.; TANG J C.; VELLEKAMP G J

Number of Countries: 077 Number of Patents: 001

Patent Family:

Patent No Kind Date Week

WO 9826048 A1 19980618 199830 B

Local Applications (No Type Date): WO 97US22134 A 19971211

Priority Applications (No Type Date): US 96766835 A 19961213

* Abstract (Basic): WO 9826048 A

Novel method for purifying a virus from impurities in an aqueous preparation comprises: (a) subjecting the virus preparation to anion-exchange chromatography in which the virus is eluted from an anion-exchange chromatographic medium, and (b) subjecting the product of (a) to size exclusion chromatography in which the virus is eluted from a size exclusion chromatographic medium. Also claimed is a virus purified by the method

USE: - The method can be used to produce purified viruses useful as viral vectors for gene therapy and for vaccine development. The method can be scaled up for large-scale operation and used with a wide range of viruses, e.g. adenoviruses or pox viruses. The method is preferably used to purify recombinant adenoviruses (e.g. the known recombinant adenovirus ACON53) but can also be used for clinical isolates or attenuated vaccine strains.

Dwg 0/0

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DIALOG(R)File 351:DERWENT WPI

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011814319

WPI Acc No: 98-231229/199821

XRAM Acc No: C98-072313

Adenovirus E1-complementing cell lines for producing defective adenoviral vectors - comprising stably integrated complementation element, but lacking 5'-terminal repeat, packaging sequence and E1A promoter

Patent Assignee: MASSIE B (MASS-B); NAT RES COUNCIL CANADA (CANA)

Inventor: MASSIE B

Number of Countries: 001 Number of Patents: 001

Patent Family:

Patent No Kind Date Week

CA 2177085 A 19971027 199821 B

Local Applications (No Type Date): CA 2177085 A 19960426

Priority Applications (No Type Date): CA 2177085 A 19960426

Abstract (Basic): CA 2177085 A

An adenovirus (Ad) E1-complementing cell line comprising a stably integrated complementation element including a portion of the Ad E1 region covering the E1A and E1B genes, but lacking the 5' inverted terminal repeat, the packaging sequence and the E1A promoter. The E1A gene is under the control of a first promoter and the E1B gene is under the control of a second promoter. The complementation element gives rise to functional E1A and E1B proteins and thereby trans-complements a defective Ad vector without production of replication-competent adenovirus (RCA) by homologous recombination between the defective Ad vector and the complementation element.

USE - The cell line is used for the large scale production of infectious E1-deleted adenoviral particles which may be used e.g. in gene therapy.

ADVANTAGE - Contamination of the E1-defective stock with replication competent Ad (RCA) (as occurs with cell line 293) is minimised.

Dwg 0/2

1/27/3

DIALOG(R)File 351:DERWENT WPI

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011670042

WPI Acc No: 98-086951/199808
XRAM Acc No: C98-029484

Recombinant adenovirus production in packaging cells with recovery from supernatant - after natural lysis of cells, and purification, e.g. on strong anion exchanger, provides high yield of pure viruses for gene and cellular therapy

Patent Assignee: RHONE-POULENC RORER SA (RHON)

Inventor: BLANCHE F. GUILLAUME J; GUILLAUME J M

Number of Countries: 069 Number of Patents: 004

Patent Family:

Patent No Kind Date Week

WO 9800524 A1 19980108 199808 B

FR 2750433 A1 19980102 199809

AU 9734470 A 19980121 199825

ZA 9705823 A 19980527 199827

Local Applications (No Type Date): WO 97FR1 107 A 19970620; FR 968164 A

19960701; AU 9734470 A 19970620; ZA 975823 A 19970630

Priority Applications (No Type Date): US 9626667 A 19960925; FR 968164 A

19960701

Abstract (Basic): WO 9800524 A

Production of recombinant adenovirus (A) comprises:

(a) introducing viral DNA into a culture of packaging cells, and

(b) harvesting (A) produced after their release into the

supernatant

Also claimed are:

(1) purification of (A) from a medium by chromatography on a strong anion exchanger;

(2) (A) prepared as described above;

(3) use of iodixanol (I;

5,5'-[(2-hydroxypropane-1,3-diyl)bis(acetylaminio)]

bis[N,N'-bis(2,3-dihydroxypropyl)

-2,4,6-trinitrobenzene-1,3-dicarboxamide) for purification of

adenovirus, and

(4) purification of adenovirus from medium by:

(i) ultracentrifugation;

(ii) dilution or dialysis, and

(iii) anion-exchange chromatography.

USE - (A) are used as gene transfer vectors for gene or cellular therapy, e.g. for expression of blood factors, enzymes, hormones, lymphokines, tumour suppressors, antisense sequences and antigens for vaccination.

Typical applications are in cases of inherited or neurodegenerative disease, cancer, dyslipoproteinaemia, and virus (e.g. human immunodeficiency virus) infection.

(A) are administered, e.g. topically, orally or by injection,

especially in doses of 104-1014 (especially 106-1010) plaque-forming units (pfu).

ADVANTAGE - The method produces, very rapidly and on an industrial scale, stocks of virus of high quality (as regards purity, stability, morphology and infectivity). Harvesting need not be precisely timed (contrast the intracellular method); maximum recovery is ensured, and the kinetics of (A) release is easily monitored by analysing samples of supernatant without pretreatment.

No cell lysis is required (so there is no risk of generating virus-containing aerosols, no contamination by cell debris and better maturation to a homogenous population of virus particles).

(I) is a non-toxic alternative for caesium chloride for density-gradient ultracentrifugation.

Dwg. 0/12

1/27/4

DIALOG(R)File 351:DERWENT WPI

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011099606

WPI Acc No: 97-077531/199707

XRAM Acc No: C97-024970

New packaging cells and nucleic acids for recombinant adenovirus - have no overlapping sequences, prevents homologous recombination, for use in gene therapy and vaccination

Patent Assignee: INTROGENE BV (INTR-N); RIJKSUNIV LEIDEN (UYLE-N)

Inventor: BOUT A; FALLAUX F J; HOEBEN R C; VALERIO D; VAN DER EB A J

Number of Countries: 072 Number of Patents: 003

Patent Family:

Patent No Kind Date Week

WO 9700326 A1 19970103 199707 B

AU 9660182 A 19970115 199718

EP 833934 A1 19980408 199818

Local Applications (No Type Date): WO 96NL244 A 19960614; AU 9660182 A

19960614; EP 96917735 A 19960614; WO 96NL244 A 19960614

Priority Applications (No Type Date): EP 95201728 A 19950626; EP 95201611 A

19950615

Abstract (Basic): WO 9700326 A

A new recombinant nucleic acid (NA) mol. (I) based on, or derived from, an adenovirus is new, having at least 1 functional: encapsidating signal; and inverted terminal repeat or a fragment or deriv., and having no overlapping sequences which allow for homologous recombination leading to replication-competent virus in a cell to which it is transferred. Also new are: (a) a recombinant NA mol. formed as a result of NA polymerase on (I); (b) a packaging cell for packaging adenovirus-derived NA mols. and which has at least 1 (I) which enable the cell to express adenoviral gene prods. derived from at least the E1A region; (c) a recombinant NA mol. based on, or derived from, an

adenovirus, having a deletion of nucleotides (nt) 459-1713 or 459-3510 of the E1 region; (d) a packaging cell harbouring nt 80-5788 (deposited under number 95062101 at the ECACC), 459-1713 or 459-3510 of human adenovirus 5; and (e) an adenovirus-like particle contg. (f).

USE - (f) and the cells are used in gene therapy to treat genetic disorders, tumours, acquired diseases and (auto)immune diseases. The packaging system is used to produce minimal adenovirus vectors which are used in gene therapy and in vaccination.

ADVANTAGE - The packaging cells have no overlapping sequences with a new basic vector and so are suited for safe, large-scale prodn. of recombinant adenoviruses. The present cells avoid the prodn. of replication-competent adenovirus and/or interference with the immune system.

Dwg.0/19

1/27/5

DIALOG(R)File 351:DERWENT WPI

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010742549

WPI Acc No: 96-239504/199624

XRAM Acc No: C96-076498

Hybrid adenovirus-adeno-associated virus for gene therapy - comprises adenovirus portion, 5' and 3' ITR sequences from AAV and a selected transgene, e.g. CFTR or LDL

Patent Assignee: UNIV PENNSYLVANIA (U)TYPE-N)

Inventor: FISHER K.J., KELLEY W.M., WILSON J.M

Number of Countries: 068 Number of Patents: 004

Patent Family:

Patent No Kind Date Week

WO 9613598 A2 19960509 199624 B

AU 9644055 A 19960523 199635

WO 9613598 A3 19960815 199641

EP 797678 A1 19971001 199744

Local Applications (No Type Date): WO 95US14018 A 19951027, AU 9644055 A

19951027, WO 95US14018 A 19951027, EP 95942840 A 19951027, WO 95US14018

A

19951027

Priority Applications (No Type Date): US 94331384 A 19941028

Abstract (Basic): WO 9613598 A

A novel recombinant hybrid virus (f) comprises: (a) DNA sequences of the 5' inverted terminal repeat (ITR) of an adenovirus and the 5' adenovirus packaging/enhancer domain; (b) DNA sequences of the 5' adeno-associated virus (AAV) ITR sequences; (c) a gene encoding a selected protein operatively linked to regulatory sequences directing expression of the protein in a target cell in vivo or in vitro; (d) DNA sequences of the 3' AAV ITR sequences; (e) DNA sequences of the 3' adenovirus ITR sequences; where the virus is replication-defective and

is provided with a sufficient portion of the genome of the adenovirus to permit infection of the target cell.

USE - (f) may be used in a composition used in the delivery and stable integration of a selected gene into the chromosome of a target cell (claimed), i.e. gene therapy of cystic fibrosis and familial hypercholesterolaemia. The transduced cell may be used for the large scale production of recombinant AAV (claimed).

Dwg.0/7

1/27/6

DIALOG(R)File 351:DERWENT WPI

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010150829 **Image available**

WPI Acc No: 95-052081/199507

XRAM Acc No: C95-023922

Adenovirus vectors for producing genetically engineered cells - e.g. beta cells that secrete insulin in response to glucose

Patent Assignee: UNIV TEXAS SYSTEM (TEXA)

Inventor: GERARD R.D.; NEWGARD C.B

Number of Countries: 055 Number of Patents: 004

Patent Family:

Patent No Kind Date Week

WO 9500644 A1 19950105 199507 B

AU 9471799 A 19950117 199521

EP 707646 A1 19960424 199621

AU 687836 B 19980305 199820

Local Applications (No Type Date): WO 94US7321 A 19940628, AU 9471799 A

19940628, EP 94920831 A 19940628, WO 94US7321 A 19940628, AU 9471799 A

19940628

Priority Applications (No Type Date): US 9384742 A 19930628

Abstract (Basic): WO 9500644 A

An adenovirus vector construct (f) comprises a recombinant insert (fI) including an expression region (fII) which is under the control of a promoter and includes a coding region that encodes 1 glucose transport protein, glucose phosphorylating protein or a fragment of these. Also claimed are: (A) a recombinant host cell (fV) incorporating (f), (B) an adenoviral virion contg. (f), (C) a compsn. comprising (f) in a buffer, and (D) a method for providing glucose-responsive insulin secreting capability to a cell, comprising (a) obtaining an insulin producing cell, and (b) expressing a GLUT-2 glucose transporter or a glucokinase enzyme or both in the cell.

USE - Using the methods, recombinant DNA technology and cell culture method is possible to engineer an 'artificial beta cell' that secretes insulin in response to glucose. The beta cells that are produced can be used in a variety of applications, e.g. in the detection of diabetes-associated antigens, in the clinical treatment of IDDM and even in the large scale production of correctly-folded

insulin. The method is used to inhibit hexolase activity in the cell pref. a islet beta cell, located within a mammal with NIDDM-like syndrome.

Dwg 0/8

1/27/9

DIALOG(R)File 351:DERWENT WPI

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007941509

WPI Acc No: 89-206621/198928

Related WPI Acc No: 91-038675

XRAM Acc No: C89-091780

Modified human cells with extended culture life - contg. E1 adenovirus or SV40 T antigen system, providing high prodn. of cell products e.g. tissue plasminogen activator

Patent Assignee: INVITRON CORP (INVI-N)

Inventor: HSU C, MCGROGAN M P, SIMONSEN C C

Number of Countries: 013 Number of Patents: 002

Patent Family:

Patent No Kind Date Week

WO 8905862 A 19890629 198928 B

AU 8929212 A 19890719 198941

Local Applications (No Type Date): WO 88US4415 A 19881209

Priority Applications (No Type Date): US 87130824 A 19871209

Abstract (Basic): WO 8905862 A

Differentiated human cells which generate a prod. (1) are modified to extend their life in culture without making them tumorigenic by (1) transfecting them with the E1a gene of adenovirus or an SV40 T-antigen expression system (or their equivs.); (2) culturing the cells and selecting tightly-packed foci; (3) cloning cells from these foci and (4) screening cells for (1) generation.

Also new are such cells with increased doubling rate and extended life.

Pref. the cells are epithelial, esp. colon mucosal cells which produce tissue plasminogen activator (t-PA).

USE/ADVANTAGE - These cells are used for large-scale prodn. of (1), which can be natural or recombinant prods. They can be grown under standard conditions; will survive more passages than normal cells without becoming senescent, and show no undesirable morphological changes.

1/27/10

DIALOG(R)File 351:DERWENT WPI

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007813355

WPI Acc No: 89-078467/198911

XRAM Acc No: C89-034818

Prodn. of recombinant human Factor-VIII-C - using animal cells

transformed with a vector contg. the gene for Factor VIII:C and a promoter

Patent Assignee: CHEMO SERO THERAPEUTIC RES INST (KAGA), TEIJIN LTD (TEIJ)

)

Inventor: MASUDA K, SUGIYAMA T, TAJIMA Y, YONEMURA H

Number of Countries: 015 Number of Patents: 006

Patent Family:

Patent No Kind Date Week

EP 306968 A 19890315 198911 B

AU 8822003 A 19890316 198924

JP 3087173 A 19910411 199121

EP 306968 B1 19931201 199348

DE 3885983 G 19940113 199403

ES 2061582 T3 19941216 199505

Local Applications (No Type Date): EP 88114769 A 19880909, JP 8885454 A 19880408, EP 88114769 A 19880909, DE 3885983 A 19880909, EP 88114769 A 19880909, EP 88114769 A 19880909

Priority Applications (No Type Date): JP 8885454 A 19880408, JP 87225147 A 19870910

Abstract (Basic): EP 306968 A

A transformant of animal cells is claimed which is produced by transforming animal cells with an expression vector contg. a gene encoding natural type active human Factor VIII:C (I) and at least one promoter upstream.

The promoter may be a hybrid promoter derived from an adenovirus promoter region and the SV40 promoter region. The expression vector may also contain a selectable marker gene, e.g. dihydrofolate reductase (dhfr) gene. (I) may be a protein in which ARG-740 of the carboxyl terminus of the H chain is directly bonded by a peptide bond to Glu-1649 of the amino terminus of the L chain. Cultivation of the transformant may be carried out in medium contg. von Willebrand factor, albumin, polyethylene glycol, sodium selenite, epsilon-aminocaproic acid, phenylmethanesulphonyl fluoride, aproinin or cyclodextrins.

USE/ADVANTAGE - The transformants can constantly and continuously produce (I) in high yield and can grow rapidly in an inexpensive medium, and can propagate in a permanent manner. It is possible on a commercial scale to produce a recombinant Factor VIII:C which is considered to correspond to the smallest species of active and intact Factor VIII:C molecules in the human blood plasma. The recombinant Factor VIII:C produced is useful for the treatment of bleeding in hemophilia A patients who are deficient in Factor VIII:C.

0/0

Abstract (Equivalent): EP 306968 B

A method for producing a protein having human Factor VIII:C activity and consisting of the heavy and light chain of human Factor VIII:C, by culturing, in a nutrition medium, transformed animal cells

containing an expression vector comprising - the DNA sequences corresponding to the heavy and light chain which are linked to a signal peptide sequence - at least one promoter upstream thereof, and - at least one enhancer and recovering the protein having human Factor VIII: C activity accumulated in the nutrition medium characterised in that the cultivation is carried out by adding to the nutrition medium, albumin, polyethylene glycol, sodium selenite, aminocaproic acid, phenylmethanesulfonyl fluoride (PMSF), aprotinin or cyclodextrins.

Dwg.0/7

? b 155,5;exs

05aug98 07:30:57 User208669 Session D1236.7

\$9.75 1,000 DialUnits File351

\$3.00 12 Type(s) in Format 26

\$26.80 8 Type(s) in Format 27

\$29.80 20 Types

\$39.55 Estimated cost File351

\$39.55 Estimated cost this search

\$73.77 Estimated total session cost 9,056 DialUnits

SYSTEM:OS - DIALOG OneSearch

File 155:MEDLINE(R) 1966-1998/Sep W4

(c) format only 1998 Dialog Corporation

File 5:BIOSIS PREVIEW(S(R) 1969-1998/JUL W4

(c) 1998 BIOSIS

Set Items Description

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Executing TD450

16247 ADENO

641273 VIRUS?

96 ADENO(W)VIRUS?

33516 ADENOVIR?

190038 SCALE?

S1 53 (ADENO(W)VIRUS? OR ADENOVIR?) AND SCALE?

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...completed examining records

S2 38 RD (unique items)

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2/7/2 (Item 2 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

09523199 98211339

Factors influencing recombinant adeno-associated virus production.

Salvetti A; Orevé S; Chadeuf G; Favre D; Chereil Y; Champion-Arnaud P;

David-Arneline J; Moullet P

Laboratoire de Therapie Genique, CHU Hotel-DIEU, Nantes, France.
Hum Gene Ther (UNITED STATES) Mar 20 1998, 9 (5) p695-706, ISSN
1043-0342 Journal Code: A12

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Recombinant adeno-associated virus (rAAV) is produced by transfecting cells with two constructs: the rAAV vector plasmid and the rep-cap plasmid. After subsequent adenoviral infection, needed for rAAV replication and assembly, the virus is purified from total cell lysates through CsCl gradients. Because this is a long and complex procedure, the precise titration of rAAV stocks, as well as the measure of the level of contamination with adenovirus and rep-positive AAV, are essential to evaluate the transduction efficiency of these vectors *in vitro* and *in vivo*.

Our vector core is in charge of producing rAAV for outside investigators as part of a national network promoted by the Association Francaise contre les Myopathies/Genethon. We report here the characterization of 18 large-scale rAAV stocks produced during the past year. Three major improvements were introduced and combined in the rAAV production procedure: (i) the titration and characterization of rAAV stocks using a stable rep-cap HeLa cell line in a modified Replication Center Assay (RCA); (ii) the use of different rep-cap constructs to provide AAV regulatory and structural proteins; (iii) the use of an adenoviral plasmid to provide helper functions needed for rAAV replication and assembly. Our results indicate that: (i) rAAV yields ranged between 10(11) to 5 x 10(12) total particles; (ii) the physical particle to infectious particle (measured by RCA) ratios were consistently below 50 when using a rep-cap plasmid harboring an ITR-deleted AAV genome; and the physical particle to transducing particle ratios ranged between 400 and 600; (iii) the use of an adenoviral plasmid instead of an infectious virion did not affect the particles or the infectious particles yields nor the above ratio. Most of large-scale rAAV stocks (7/9) produced using this plasmid were free of detectable infectious adenovirus as determined by RCA; (iv) all the rAAV stocks were contaminated with rep-positive AAV as detected by RCA. In summary, this study describes a general method to titrate rAAV, independently of the transgene and its expression, and to measure the level of contamination with adenovirus and rep-positive AAV. Furthermore, we report a new production procedure using adenoviral plasmids instead of virions and resulting in rAAV stocks with undetectable adenovirus contamination.

2/7/6 (Item 6 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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09099835 97234483

Generation, validation, and large scale production of adenoviral recombinants with large size inserts such as a 6.3 kb human dystrophin cDNA.

Jani A; Lochmuller H; Acsadi G; Simoneau M; Huard J; Garnier A; Karpati G

; Massie B

Montreal Neurological Institute, McGill University, Quebec, Canada.

J Virol Methods (NETHERLANDS) Mar 1997, 64 (2) p111-24, ISSN 0166-0934 Journal Code: HQR

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Human, serotype 5 (Ad 5), replication-defective recombinant adenoviruses (AdVs) expressing a 6.3 kb partial dystrophin cDNA (Becker) under the control of either the CMV early or the RSV LTR promoter/enhancer in combination with various polyadenylation sequences (polyA), were developed for gene transfer studies aimed at Duchenne muscular dystrophy. Based on previous experience, a strategy for generation, screening and validation of AdVs with relatively large size gene expression cassette inserts was established. Here we focus on some aspects of stability and safety of such AdVs as gene therapeutic tools based on relevant molecular biological methods. Furthermore, the quality of our best AdV-minidystrophin construct was validated following its large scale production and purification as well as its delivery in mdx mice. These results are of interest for establishing other AdVs, where the combined length of a tissue specific promoter, the gene of interest and the polyA sequences reach the upper limit of the packaging capacity of first generation AdVs.

2/7/10 (Item 10 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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08666352 96236790

A new strategy for large-scale preparation of high-titer recombinant adeno-associated virus vectors by using packaging cell lines and sulfonated cellulose column chromatography.

Tamayose K, Hirai Y, Shimada T

Department of Biochemistry and Molecular Biology, Nippon Medical School, Tokyo, Japan.

Hum Gene Ther (UNITED STATES) Mar 1 1996, 7 (4) p507-13, ISSN 1043-0342 Journal Code: A12

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The extensive testing of adeno-associated virus (AAV) as a vector for human gene therapy has been hampered by low efficiency of the current packaging system, which is based on transient transfection with plasmid DNAs and infection with adenovirus in permissive cells. In an effort to resolve this problem, HeLa cell-based packaging cell lines were established. These packaging cells carry multiple copies of the AAV genome lacking the inverted terminal repeat (ITR) sequences. The AAV genes were silent in these cells but inducibly expressed by adenovirus infection. When the AAV vector plasmid containing the neor gene flanked by the ITRs was also integrated into these cells, efficient production of the recombinant AAV particles occurred after adenovirus infection. AAV vector particles in

cell lysates could be concentrated by sulfonated cellulose column chromatography. Using the packaging cells and the column chromatography technique, it is possible to prepare AAV vectors with the titer of higher than 10(8) cfu/ml or 5 x 10(10) particles/ml. This new strategy should be useful for testing AAV vectors in vivo.

2/7/14 (Item 14 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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08161031 95200732

Scale-up of the adenovirus expression system for the production of recombinant protein in human 293S cells.

Garnier A, Cote J, Nadeau I, Kamen A, Massie B

Institut de recherche en biotechnologie, CNRC, Montreal, Quebec, Canada. Cytochemistry (NETHERLANDS) 1994, 15 (1-3) p145-55, ISSN 0920-9069 Journal Code: AT5

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Human 293S cells, a cell line adapted to suspension culture, were grown to 5 x 10(6) cells/mL in batch with calcium-free DMEM. These cells, infected with new constructions of adenovirus vectors, yielded as much as 10 to 20% recombinant protein with respect to the total cellular protein content. Until recently, high specific productivity of recombinant protein was limited to low cell density infected cultures of no more than 5 x 10(5) cells/mL. In this paper, we show with a model protein, Protein Tyrosine Phosphatase 1C, how product yield can be maintained at high cell densities of 2 x 10(6) cells/mL by a medium replacement strategy. This allows the production of as much as 90 mg/L of active recombinant protein per culture volume. Analysis of key limiting/inhibiting medium components showed that glucose addition along with pH control can yield the same productivity as a medium replacement strategy at high cell density in calcium-free DMEM. Finally, the above results were reproduced in 3L bioreactor suspension culture thereby establishing the scalability of this expression system. The process we developed is used routinely with the same success for the production of various recombinant proteins and viruses.

2/7/27 (Item 1 from file: 5)

DIALOG(R)File 5:BIOSIS PREVIEWS(R)

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14107989 BIOSIS Number: 01107989

A novel packaging cell line (PER.C6) for efficient production of RCA-free batches of E1-deleted recombinant adenoviral vectors

Boutl A, Fallaux F J, Hehir K, Auger C, Keegan J, Van Der Velde I, Boesen

J J B, Van Der Eb A J, Hoeven R C, Valerio D

Introgene BV, Leiden, Netherlands

Cancer Gene Therapy 4 (6 CONF. SUPPL.) 1997, S32-S33.

Full Journal Title: Sixth International Conference on Gene Therapy of

AR355.56

RB/55.8.13

Not used

Cancer, San Diego, California, USA, November 20-22, 1997. Cancer Gene Therapy

ISSN: 0929-1903

Language: ENGLISH

Print Number: Biological Abstracts/RRM Vol. 050 Iss. 003 Ref. 041901

2/7/28 (Item 2 from file: 5)

DIALOG(R)File: 5:BIOSIS PREVIEWS(R)

(c) 1998 BIOSIS. All rts. reserv.

13199625 BIOSIS Number: 99199625

Complementation cell lines for viral vectors to be used in gene therapy

Mehlti M

Transgene S.A., 11 Rue de Molshem, 67000 Strasbourg, France

Cytotechnology 19 (1). 1995-1996. 43-54.

Full Journal Title: Cytotechnology

ISSN: 0920-9069

Language: ENGLISH

Print Number: Biological Abstracts Vol. 102 Iss. 009 Ref. 131632

Viral vectors provide a highly efficient method for the transfer of foreign genes into a variety of quiescent or dividing eukaryotic cells from many animal origins. While recombinant vectors derived from an increasing number of mammalian viruses (herpes simplex virus, autonomous and non-autonomous parvoviruses, poxviruses, retroviruses, adenoviruses available today, vectors based on murine retroviruses and human adenoviruses constitute preferential candidates for the delivery of marker or therapeutic genes into human somatic cells. The availability of such vectors has made possible the recent transition of human gene therapy from laboratory benches to clinical settings. Most current recombinant vectors have been generated by deleting essential viral genes in order to make space available for the introduction of passenger genes. Such vectors are therefore unable to replicate in the absence of these critical gene products and their production relies on the development of stable complementation cell lines providing in trans the missing viral functions. Although complementation (or packaging) cell lines are available for both adenovirus and retrovirus vectors, their respective drawbacks still limit their use to research applications and phase I clinical trials. The future success or failure of human gene therapy will therefore rely on the production of improved generations of packaging cell lines that can produce safer and more efficient vectors which are fully adapted to large scale production and clinical applications.

2/7/30 (Item 4 from file: 5)

DIALOG(R)File: 5:BIOSIS PREVIEWS(R)

(c) 1998 BIOSIS. All rts. reserv.

13161267 BIOSIS Number: 99161267

Improvement of recombinant protein production with the human adenovirus-293S expression system using fed-batch strategies

Nadeau J, Garnier A, Cote J, Massie B, Chavarie C, Kamen A
Inst. recherche biotechnol., CNRC, 6100 avenue Royalmount, Montreal, PQ
H4P 2R2, Canada

Biotechnology and Bioengineering 51 (6). 1996. 613-623.

Full Journal Title: Biotechnology and Bioengineering

ISSN: 0006-3592

Language: ENGLISH

Print Number: Biological Abstracts Vol. 102 Iss. 007 Ref. 109398

The human adenovirus/293S cell expression system is used for the production of either recombinant protein or adenovirus vectors for use in gene therapy. In this work, the production of protein tyrosine phosphatase (PTP1C) was used as a model for the scale-up of both applications. Maximum specific production of 30 to 45 μg of active protein/10-6 cells was maintained upon infection with adenovirus vectors at cell densities between 2 times 10-6 to 3 times 10-6 cells/mL in a 3.5-L bioreactor. This was achieved by resuspending the culture in fresh medium at infection time. The pH was kept at 7.0 throughout the experiment and, at 24 h postinfection, glucose and essential amino acids were added. Attempts to replace the complete change of medium at the time of infection with nutrient supplementation of the used medium led to lower production levels, suggesting that protein expression was limited not by the absence of a key nutrient but by inhibitory factors. Two potentially inhibitory factors were investigated: lactic acid accumulation and increased osmolality. Medium acidification such as that which would be brought about by lactic acid accumulation was shown to depress PTP1C production. The lactate molecule itself decreased the cell viability when added in concentrations of 20 mM or more. But the specific productivity was affected at higher lactate concentrations of 40 mM or more. Additions of glucose, amino acids, and NaHCO_3 used to control pH, led to increases in osmolality. Osmolarities above 400 mOsm lowered cell density. However, specific production was not significantly affected below 500 mOsm. But, at 500 mOsm, PTP1C production peak was shifted from 48 to 72 hpi. Because of the cell loss, this per cell yield increase did not translate into higher volumetric production. When glucose concentrations were kept at 5 mM by fed-batch addition, lactate production and increases in osmolality were reduced. In shake flasks, this method permitted maximum production with cells resuspended either in fresh or spent medium at infection. This fed-batch process was implemented successfully at the 3.5-L scale. Fed-batch with glucose may provide a means to increase infected-cell density beyond 3 times 10-6 cells/mL.

2/7/38 (Item 12 from file: 5)

DIALOG(R)File: 5:BIOSIS PREVIEWS(R)

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3125676 BIOSIS Number: 70075583

PROPAGATION OF MAMMALIAN CELLS AND OF VIRUS IN A SELF REGULATING FERMENTER

FOEHRING B, TJIA S T, ZENKE W M, SAUER G, DOERFLER W
DEP. PATHOL., RUTGERS MED. SCH, PISCATAWAY, N.J. 08854, USA.
PROC SOC EXP BIOL MED 164 (2). 1980. 222-228. CODEN: PSEBA
Full Journal Title: Proceedings of the Society for Experimental Biology
and Medicine

Language: ENGLISH

A number of different mammalian cell lines were cultivated in large scale
batches in a fermenter which controlled the pH value of the medium. Acid
produced due to cellular metabolism was titrated by the addition of NaOH.
It was shown that the ensuing increase in NaCl concentration had no
deleterious effects on cell growth, as long as this increase did not exceed
10% of the regular NaCl concentration in the medium. The production of
human adenovirus type 2 (Ad2) in large scale suspension cultures of [human
oral carcinoma] KB cells was strongly pH dependent; optimal yields were
obtained at pH 7.35. Under controlled conditions the pH value in an
Ad2-infected culture of KB cells dropped from 8 to 6.9 within a period of
35 h. Monkey [African green, kidney] Vero cells latently infected with the
papova HD virus strain of stump-tailed macaque virus were propagated on a
beaded microcarrier in the fermenter. Such microcarrier complexes were
capable of producing viral DNA.

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Set Items Description
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S2 38 RD (unique items)
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53 S1
38 S2
S3 15 S1 NOT S2
? t s3 7/8

37/8 (Item 8 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)
(c) 1998 BIOSIS. All rts. reserv.
11535792 BIOSIS Number: 98135792
Scale-up of the adenovirus expression system for the production of
recombinant protein in human 293S cells
Garnier A, Cote J, Nadeau I, Kamen A, Massie B
Inst. Recherche en Biotechnologie, CNRC, 6100 Royalmount, Montreal, PQ
H4P 2R2, Canada
Cytotechnology 15 (1-3). 1994. 145-155.
Full Journal Title: Cytotechnology
ISSN: 0920-9069
Language: ENGLISH
Print Number: Biological Abstracts Vol. 099 Iss. 007 Ref. 092349
Human 293S cells, a cell line adapted to suspension culture, were grown
to 5 times 10-6 cells/mL in batch with calcium-free DMEM. These cells,

infected with new constructions of adenovirus vectors, yielded as much as
10 to 20% recombinant protein with respect to the total cellular protein
content. Until recently, high specific productivity of recombinant protein
was limited to low cell density infected cultures of no more than 5 times
10-5 cells/mL. In this paper, we show with a model protein, Protein
Tyrosine Phosphatase 1C-50, how high product yield can be maintained at
high cell densities of 2 times 10-6 cells/mL by a medium replacement
strategy. This allows the production of as much as 90 mg/L of active
recombinant protein per culture volume. Analysis of key limiting/inhibiting
medium components showed that glucose addition along with pH control can
yield the same productivity as a medium replacement strategy at high cell
density in calcium-free DMEM. Finally, the above results were reproduced in
3L bioreactor suspension culture thereby establishing the scalability of
this expression system. The process we developed is used routinely with the
same success for the production of various recombinant proteins and
viruses.

Set Items Description
S1 53 (ADENO(W)VIRUS? OR ADENOVIR?) AND SCALE?
S2 38 RD (unique items)
S3 15 S1 NOT S2
? s adenovir? or adeno(w)virus?
33516 ADENOVIR?
16247 ADENO
641273 VIRUS?
96 ADENO(W)VIRUS?
S4 33569 ADENOVIR? OR ADENO(W)VIRUS?
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S5 51315 DETERGENT?
? s s4 and s5
33569 S4
51315 S5
S6 111 S4 AND S5
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S7 219292 LYS???
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? s s6 and s7
111 S6
219292 S7
S8 11 S6 AND S7
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Set Items Description
S1 53 (ADENO(W)VIRUS? OR ADENOVIR?) AND SCALE?

S2 38 RD (unique items)
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 S4 33569 ADENOVIR? OR ADENO(W)VIRUS?
 S5 51315 DETERGENT?
 S6 111 S4 AND S5
 S7 219292 LYS???
 S8 11 S6 AND S7
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 26583 TRITON
 5755 TWEEN
 1126 BRJ
 214 NP40
 S9 32677 TRITON OR TWEEN OR BRJ OR NP40
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 S4 33569 ADENOVIR? OR ADENO(W)VIRUS?
 S5 51315 DETERGENT?
 S6 111 S4 AND S5
 S7 219292 LYS???
 S8 11 S6 AND S7
 S9 32677 TRITON OR TWEEN OR BRJ OR NP40
 ? s s4 and s9
 33569 S4
 32677 S9
 S10 40 S4 AND S9
 ? rd
 ...completed examining records
 S11 29 RD (unique items)
 ? t s107/12 28

10/7/12 (Item 12 from file: 155)
 DIALOG(R)File 155: MEDLINE(R)
 (c) format only 1998 Dialog Corporation. All rts. reserv.
 04738653 86033943
 Binding of adenovirus and its external proteins to Triton X-114.
 Dependence on pH.
 Seth P. Willingham M.C; Pastan I
 J Biol Chem (UNITED STATES) Nov 25 1985, 260 (27) p14431-4, ISSN
 0021-97258 Journal Code: HIV
 Languages: ENGLISH
 Document type: JOURNAL ARTICLE
 35S-labeled adenovirus type 2 (Ad2) (10 ng/ml) was incubated with 1%
 Triton X-114 at various pH values varying from 3.0 to 8.0. The detergent

phase was separated from the aqueous phase by centrifugation, and the amounts of Ad2 were determined in the two phases. At pH 7.0-8.0, less than 5% of Ad2 was associated with the detergent phase; at pH 5.0 or below, about 60% of Ad2 was associated with the detergent phase. When a mixture of 35S-labeled capsid proteins was used at pH 7.0, 60-70% of the total proteins were associated with the detergent at pH 5.0, but less than 5% of the proteins interacted with detergent at pH 7.0. Among the three major external proteins (hexon, penton base, and fiber), penton base had the highest association with Triton X-114 at pH 5.0. Both intact virus and the capsid proteins that were associated with Triton X-114 at pH 5.0 were released into the aqueous phase on subsequent incubation at pH 7.0. On the basis of these results, it is suggested that mildly acidic pH induces amphiphilic properties in adenovirus capsid proteins and may help Ad2 escape from acidic endocytic vesicles.

10/7/28 (Item 12 from file: 5)
 DIALOG(R)File 5: BIOSIS PREVIEWS(R)
 (c) 1998 BIOSIS. All rts. reserv.
 5289037 BIOSIS Number: 81056344
 BINDING OF ADENOVIRUS AND ITS EXTERNAL PROTEINS TO TRITON X-114
 DEPENDENCE ON PH
 SETH P. WILLINGHAM M.C; PASTAN I
 LAB. OF MOLECULAR BIOL., DIVISION OF CANCER BIOL. AND DIAGNOSIS, NATL. CANCER INST., NATL. INST. OF HEALTH, BETHESDA, MD. 20205.
 J BIOL CHEM 260 (27). 1985. 14431-14434. CODEN: JBCHA
 Full Journal Title: Journal of Biological Chemistry
 Language: ENGLISH
 35S-labeled adenovirus type 2 (Ad2) (10 ng/ml) was incubated with 1% Triton X-114 at various pH values varying from 3.0 to 8.0. The detergent phase was separated from the aqueous phase by centrifugation, and the amounts of Ad2 were determined in the two phases. At pH 7.0-8.0, less than 5% of Ad2 was associated with the detergent phase; at pH 5.0 or below, about 60% of Ad2 was associated with the detergent phase. When a mixture of 35S-labeled capsid proteins was used at pH 7.0, 60-70% of the total proteins were associated with the detergent at pH 5.0, but less than 5% of the proteins interacted with detergent at pH 7.0. Among the three major external proteins (hexon, penton base, and fiber), penton base had the highest association with Triton X-114 at pH 5.0. Both intact virus and the capsid proteins that were associated with Triton X-114 at pH 5.0 were released into the aqueous phase on subsequent incubation at pH 7.0. On the basis of these results, it is suggested that mildly acidic pH induces amphiphilic properties of adenovirus capsid proteins and may help Ad2 escape from acidic endocytic vesicles.
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\$1.00 5 Type(s) in Format 7
\$1.00 72 Types
\$5.00 Estimated cost File155
\$8.74 1.665 DialUnits File5
\$0.00 46 Type(s) in Format 6
\$8.70 6 Type(s) in Format 7
\$8.70 52 Types
\$17.44 Estimated cost File5
OneSearch, 2 files, 3.000 DialUnits FileOS
\$22.44 Estimated cost this search
\$96.21 Estimated total session cost 12.056 DialUnits
Logoff: level 98.07.06 D 07:45:03

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05aug98 08:18:34 User208669 Session D1237.1

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\$0.14 Estimated cost File1

\$0.14 Estimated cost this search

\$0.14 Estimated total session cost 0.043 DialUnits

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1 15: ABI/INFORM(R)_1971-1998/Jul W4
12 16: IAC PROMT(R)_1972-1998/Aug 05
38 34: SciSearch(R) Cited Ref Sci_1990-1998/Jul W4
3 35: Dissertation Abstracts Online_1861-1998/Aug
2 50: CAB Abstracts 1972-1998/Jun
1 51: Food Sci.&Tech.Abs_1969-1998/Jul
1 53: FOODLINE(R): Food Science &
    Technology_1972-1998/Aug 03
1 64: Global Mobility Database (R)_1965-1998/Jun
1 67: World Textiles_1970-1998/Jul
25 73: EMBASE_1974-1998/Aug W1
10 76: Life Sciences Collection_1982-1998/Jun
5 94: JICST-EPlus_1985-1998/May W4
1 96: FLINDEX_1973-1998/Jun
1 98: General Sci.Abs/Full-Text_1984-1998/Jun
5 103: Energy SciTec_1974-1998/Jul B1
2 108: Aerospace Database_1962-1998/July

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Examined 50 files

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20 144: Pascal_1973-1998/Jun
7 148: IAC Trade & Industry Database_1976-1998/Aug 05
20 155: MEDLINE(R)_1966-1998/Sep W4
1 156: Toxline(R)_1965-1998/Jul
1 172: EMBASE Alert_1998/Aug W2
3 180: Federal Register_1985-1998/Aug 04
2 266: FEDRIP_1998/Jun
15 315: ChemEng & Biotec Abs_1970-1998/Aug
3 340: CLAIMS(R)/US Patent_1950-98/Jul 28
Examined 100 files
4 347: JAPIO_Oct 1976-1998/Mar (UPDATED 980630)
38 348: EUROPEAN PATENTS_1978-1998/Jul W3-

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12 351: DERWENT WPL_1963-1998/UD=9830;UP=9827;UM=9825

1 377: Derwent Drug File_1983-1998/Jul W4

1 434: SciSearch(R) Cited Ref Sci_1974-1989/Dec

1 481: Delphes Eur Bus 80-1998/Jul W3

3 624: McGraw-Hill Publications_1985-1998/Aug 04

6 636: IAC Newsletter DB(TM)_1987-1998/Aug 05

1 649: IAC NEWSWIRE ASAP(TM)_1998/Aug 05

7 653: US Pat.Fulltext_1980-1989

192 654: US Pat.Full_1990-1998/Jul 28

1 764: BCC Market Research_1989-1998/Jun

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N1 192 654: US Pat.Full_1990-1998/Jul 28
N2 38 34: SciSearch(R) Cited Ref Sci_1990-1998/Jul W4
N3 38 348: EUROPEAN PATENTS_1978-1998/Jul W3-
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N5 20 144: Pascal_1973-1998/Jun
N6 20 155: MEDLINE(R)_1966-1998/Sep W4
N7 16 8: Ei Compendex(R)_1970-1998/Aug W4
N8 15 315: ChemEng & Biotec Abs_1970-1998/Aug
N9 12 5: BIOSIS PREVIEWS(R)_1969-1998/JUL W4
N10 12 16: IAC PROMT(R)_1972-1998/Aug 05
39 files have one or more items, file list includes 145 files.

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S BIOREACTOR? AND ADENO?

Ref Items File

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N11 12 351: DERWENT WPL_1963-1998/UD=9830;UP=9827;UM=9825
N12 10 76: Life Sciences Collection_1982-1998/Jun
N13 7 148: IAC Trade & Industry Database_1976-1998/Aug 05
N14 7 653: US Pat.Fulltext_1980-1989
N15 6 636: IAC Newsletter DB(TM)_1987-1998/Aug 05
N16 5 94: JICST-EPlus_1985-1998/May W4
N17 5 103: Energy SciTec_1974-1998/Jul B1
N18 4 347: JAPIO_Oct 1976-1998/Mar (UPDATED 980630)
N19 3 35: Dissertation Abstracts Online_1861-1998/Aug
N20 3 180: Federal Register_1985-1998/Aug 04
39 files have one or more items, file list includes 145 files.

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- Enter P or PAGE for more -
 ? save temp
 Temp SearchSave "TD451" stored
 ? b 35;exs
 05aug98 08:20:47 User208669 Session D1237.2
 \$2.00 2.000 DialUnits File411
 \$2.00 Estimated cost File411
 \$2.00 Estimated cost this search
 \$2.14 Estimated total session cost 2.043 DialUnits

File 35:Dissertation Abstracts Online 1861-1998/Aug
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Set Items Description
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 Executing TD451
 569 BIOREACTOR?
 4513 ADENOT?
 S1 3 BIOREACTOR? AND ADENOT?
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1/5/1
 DIALOG(R)File 35:Dissertation Abstracts Online
 (c) 1998 UMI. All rts. reserv.
 01506268 ORDER NO: AADMM-08219
 MISE A L'ECHELLE DU PROCEDE DE PRODUCTION DE PROTEINES
 RECOMBINANTES A VEC
 LE SYSTEME D'EXPRESSION ADENOVIRUS ET CELLULES 293S (FRECH TEXT)
 Author: NADEAU, ISABELLE
 Degree: M.SC.A.
 Year: 1995

Corporate Source/Institution: ECOLE POLYTECHNIQUE, MONTREAL (CANADA)
 (1105)
 Directeur: CLAUDE CHAVARIE
 Source: VOLUME 34/05 of MASTERS ABSTRACTS.
 PAGE 2003. 173 PAGES
 Descriptors: ENGINEERING, CHEMICAL ; BIOLOGY, MICROBIOLOGY
 Descriptor Codes: 0542; 0410
 Language: FRENCH
 ISBN: 0-612-08219-9

Adenovirus vectors are useful for recombinant protein production and gene therapy, easily transporting heterologous genes into mammalian cells. In this work, we have used the human adenovirus/293S cells system for production of the protein: protein tyrosine phosphatase 1C (PTP1C). This protein was used as a model for both recombinant protein and adenovirus

vector production as PTP1C and viral capsid proteins are both controlled with a MLP (Major late promoter). Factorial designs were planned to identify the most influent amino acids. The best specific production (\$\mu\$mol/\$10^5\$ cells) was obtained when all essential amino acids were added during the process.

Fresh medium was used for production since the culture medium, which had supported cellular growth up to a density of \$2 \times 10^6\$ cells/ml, does not allow maximum production after infection, even with glucose and amino acid supplementation. It was shown that lactate, the major by-product of glycolysis, decreases viability and specific production. Also, glucose, amino acids and \$\text{NaHCO}_3\$ which were fed during production, increase osmolality. Higher osmolality decreased the cell density but can slightly stimulate specific production between 400 and 500 mOsm. Feeding glucose continuously minimized both lactate production and osmotic pressure. In shake flasks, fed-batch production with glucose permitted maximum production in fresh medium and good yields in spent medium. Fed-batch with glucose may then be the alternative for recombinant protein production with spent medium as well as a means to increase infectable cell density. Fed-batch production in a 3.5L bioreactor with spent medium led to a good volumic productions at \$3.5 \times 10^6\$ cells/ml and it simplified operations in bioreactor since medium replacements were omitted at infection time and during production. (Abstract shortened by UMI.)

? b 351;exs
 05aug98 08:22:17 User208669 Session D1237.3
 \$4.00 1.000 DialUnits File35
 \$2.00 1 Type(s) in Format 5
 \$0.00 3 Type(s) in Format 6
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 \$6.00 Estimated cost File35
 \$6.00 Estimated cost this search
 \$8.14 Estimated total session cost 3.043 DialUnits

File 351:DERWENT WP1 1963-1998/UD=9830;UP=9827;UM=9825
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*File 351: All images are now present. The display formats have changed for 1998. See HELP FORM 351 for more information.

Set Items Description
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 1292 BIOREACTOR?
 4818 ADENOT?
 S1 12 BIOREACTOR? AND ADENOT?
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1/27/4
 DIALOG(R)File 351:DERWENT WP1

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009393488

WPI Acc No: 93-086955/199311
Related WPI Acc No: 93-086719
XRAM Acc No: C93-038310

Cultivation of adherent mammalian cells in protein-free medium -
comprises using polyvinylformal or polyvinylbutyral as substrate
Patent Assignee: DOERR H (DOER-1)

Inventor: CINATL J

Number of Countries: 016 Number of Patents: 003

Patent Family:

*German
F102a 841m*

Patent No	Kind	Date	Week
EP 531911	A1	19930317	199311 B
EP 531911	B1	19971210	199803
ES 2111590	T3	19980316	199817

Local Applications (No Type Date): EP 92115226 A 19920905; EP 92115226 A 19920905; EP 92115226 A 19920905

Priority Applications (No Type Date): EP 91115336 A 19910911

Abstract (Basic): EP 531911 A

The cultivation of adherent mammalian cells on a polyvinylformal and/or polyvinylbutyral substrate in a protein-free medium is claimed.

DMEM F12 supplemented with trace elements, vitamin C phosphate and glutamine dipeptide or, esp. for Vero cells, a 1:1 mixt. of Hybridmax (Sigma) and SRE-199 (Sigma) plus 800 mg/ml CaCl₂ is pref. used. Other media include Ham's F10 and F12, alpha-MEM and DMEM F12 without trace elements and vitamin C derivs.

The cells are pref. cultivated, esp. without an adaptation phase, as a monolayer and are inoculated on the substrate surface at a density of at least 2 x 10 power 4 cells/cm². The cultivation can be carried out in a bioreactor constructed from the substrate or pref. from metal, glass or plastic coated with the substrate. Alternatively, the bioreactor can be filled with glass beads, steel spirals etc. coated with the substrate.

USE/ADVANTAGE - Used to cultivate cell lines which can be used, inter alia, to produce viruses and vaccines, e.g. using cells infected with polio virus or adenovirus, as well as endogenous or recombinant proteins, such as t-Pa, EPO, hGH, ICAM-1 and human lung surfactant proteins. It is esp. suitable for cultivating Vero cells. The method is simpler and more widely applicable than known procedures. Further, the polyvinylformyl substrate has optical properties equiv. to polystyrol substrates and is inexpensive.

Dwg 0/5

Abstract (Equivalent): EP 531911 B

The cultivation of adherent mammalian cells on a polyvinylformal and/or polyvinylbutyral substrate in a protein-free medium is claimed.

DMEM F12 supplemented with trace elements, vitamin C phosphate and glutamine dipeptide or, esp. for Vero cells, a 1:1 mixt. of Hybridmax

(Sigma) and SRE-199 (Sigma) plus 800 mg/ml CaCl₂ is pref. used. Other media include Ham's F10 and F12, alpha-MEM and DMEM F12 without trace elements and vitamin C derivs..

The cells are pref. cultivated, esp. without an adaptation phase, as a monolayer and are inoculated on the substrate surface at a density of at least 2 x 10 power 4 cells/cm². The cultivation can be carried out in a bioreactor constructed from the substrate or pref. from metal, glass or plastic coated with the substrate. Alternatively, the bioreactor can be filled with glass beads, steel spirals etc. coated with the substrate.

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Dwg 0/5

1/27/5

DIALOG(R)File 351:DERWENT WPI

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009107190

WPI Acc No: 92-234621/199228

XRAM Acc No: C92-105862

Producing recombinant viral vectors for gene therapy - used to transduce host cells that are e.g. adenosine deaminase-deficient
Patent Assignee: CELLCO INC (CELL-N); US DEPT OF COMMERCE (USDC)
Inventor: BLAESE R M; CULVER K W; KNAZEK R A

Number of Countries: 002 Number of Patents: 006

Patent Family:

Patent No	Kind	Date	Week
WO 9210564	A1	19920625	199228 B
AU 9191246	A	19920708	199241
EP 564539	A1	19931013	199341
JP 6500927	W	19940203	199410
AU 650711	B	19940630	199430
EP 564539	A4	19960306	199642

Local Applications (No Type Date): WO 91US9069 A 19911210; AU 9191246 A 19911210; WO 91US9069 A 19911210; WO 91US9069 A 19911210; EP 92902297 A 19911210; WO 91US9069 A 19911210; JP 92502696 A 19911210; AU 9191246 A 19911210; EP 92902297 A 19920000

Priority Applications (No Type Date): US 90627008 A 19901213

Abstract (Basic): WO 9210564 A

A method (D) for producing a high titre of recombinant viral vectors comprises: (a) inoculating the extra fibre space (EFS) of a

hollow fibre bioreactor with producer cells that release recombinant viral vectors into the EFS medium; and (b) incubating the producer cells in the bioreactor under conditions where the titre of the vectors is sufficiently high to transduce target cells at a multiplicity of infection of more than 1 recombinant viral vector per cell.

Also new are: (1) a method like (1) for producing packaged recombinant viral vectors in which a packaging cell line is used; (2) a method like (1) in which the fibre of vectors in the EFS medium is at least 10-fold higher than that produced by cells cultured in the monolayer; (3) a method that is a combination of the methods of (1) and (2); (4) a method like (1) for transducing target cells comprising contacting the cells with vectors produced in (b); (5) a compsn. comprising target cells transduced with retroviral vectors, at a concn. of at least 10%; (6) a dual bioreactor perfusion circuit comprising 2 hollow fibre bioreactors where the EFS of the first is connected to that of the second such that the circuit may be intermittently opened to allow EFS medium of the first to flow to the second EFS; and (7) a method of producing a high concn. of transduced cells comprising culturing the cells in a hollow fibre bioreactor and continuously introducing a suspension of vectors into the EFS such that a substantial percentage of the cells are transduced.

USE - The transduced cells can be used in gene therapy

Dwg.0/2

? b 177,73;:esx

05aug98 08:25:18 User208669 Session D1237.4

\$9.75 1.000 DialUnits File351

\$0.00 12 Type(s) in Format 6

\$3.00 12 Type(s) in Format 26

\$6.70 2 Type(s) in Format 27

\$9.70 26 Types

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\$19.45 Estimated cost this search

\$27.59 Estimated total session cost 4.043 DialUnits

SYSTEM:OS - DIALOG OneSearch

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File 73:EMBASE 1974-1998/Aug W1

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Set Items Description

Ref Items RT Index-term

E1 1 SW962

E2 1 SW984

E3 249 *SX

E4 1 SX AB 1316 SE

E5 1 SX ALPHA GENE

E6 0 1 SX 1032

E7 6 SX 284

E8 2 SX 3228

E9 3 SX 810

E10 31 SXA

E11 2 SXALPHA

E12 1 SXASUP

Enter P or PAGE for more

? b 155,73;:esx

05aug98 08:25:31 User208669 Session D1237.5

\$1.63 0.500 DialUnits File177

\$1.63 Estimated cost File177

\$3.88 0.500 DialUnits File73

\$3.88 Estimated cost File73

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\$33.10 Estimated total session cost 5.043 DialUnits

SYSTEM:OS - DIALOG OneSearch

File 155:MEDLINE(R) 1966-1998/Sep W4

(c) format only 1998 Dialog Corporation

File 73:EMBASE 1974-1998/Aug W1

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Set Items Description

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5004 BIOREACTOR?

530200 ADENO?

S1 45 BIOREACTOR? AND ADENO?

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S2 41 RD (unique items)

? ts27/11 28

27/11 (Item 11 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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08161031 95200732

Scale-up of the adenovirus expression system for the production of recombinant protein in human 293S cells.

Garnier A; Cote J; Nadeau J; Kamen A; Massie B

Institut de recherche en biotechnologie, CNRC, Montreal, Quebec, Canada.

Cyotechnology (NETHERLANDS) 1994, 15 (1-3) p145-55, ISSN 0920-9069

Journal Code: A15

Languages: ENGLISH

105

Document type: JOURNAL ARTICLE

Human 293S cells, a cell line adapted to suspension culture, were grown to 5×10^6 cells/mL in batch with calcium-free DMEM. These cells, infected with new constructions of adenovirus vectors, yielded as much as 10 to 20% recombinant protein with respect to the total cellular protein content. Until recently, high specific productivity of recombinant protein was limited to low cell density infected cultures of no more than 5×10^5 cells/mL. In this paper, we show with a model protein, Protein Tyrosine Phosphatase 1C, how product yield can be maintained at high cell densities of 2×10^6 cells/mL by a medium replacement strategy. This allows the production of as much as 90 mg/L of active recombinant protein per culture volume. Analysis of key limiting/inhibiting medium components showed that glucose addition along with pH control can yield the same productivity as a medium replacement strategy at high cell density in calcium-free DMEM. Finally, the above results were reproduced in 3L bioreactor suspension culture thereby establishing the scalability of this expression system. The process we developed is used routinely with the same success for the production of various recombinant proteins and viruses.

2/7/28 (Item 8 from file: 73)

DIALOG(R)File 73:EMBASE

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10101756 EMBASE No: 96263305

Improvement of recombinant protein production with the human adenovirus/293S expression system using fed-batch strategies

Nadeau I.; Garnier A.; Cote J.; Massie B.; Chavatte C.; Kamen A.

Inst. de Recherche en Biotechnologie, CNRC, 6100 avenue Royalmount, Montreal, Que. H4P 2R2 Canada

Biotechnology and Bioengineering (USA), 1996, 51/6 (613-623)

CODEN: BIBIA ISSN: 0006-3592

LANGUAGES: English SUMMARY LANGUAGES: English

The human adenovirus/293S cell expression system is used for the production of either recombinant protein or adenovirus vectors for use in gene therapy. In this work, the production of protein tyrosine phosphatase (PTP1C) was used as a model for the scale-up of both applications. Maximum specific production of 30 to 45 microg of active protein/106 cells was maintained upon infection with adenovirus vectors at cell densities between 2×10^6 to 3×10^6 cells/mL in a 3.5-L bioreactor. This was achieved by resuspending the culture in fresh medium at infection time. The pH was kept at 7.0 throughout the experiment and, at 24 h postinfection, glucose and essential amino acids were added. Attempts to replace the complete change of medium at the time of infection with nutrient supplementation of the used medium led to lower production levels, suggesting that protein expression was limited not by the absence of a key nutrient but by inhibitory factors. Two potentially inhibitory factors were investigated: lactic acid accumulation and increased osmolarity. Medium acidification such as that which would be brought about by lactic acid accumulation was

shown to depress PTP1C production. The lactate molecule itself decreased the cell viability when added in concentrations of 20 mM or more. But the specific productivity was affected at higher lactate concentrations of 40 mM or more. Additions of glucose, amino acids, and NaHCO_3 used to control pH, led to increases in osmolarity. Osmolarities above 400 mOsm lowered cell density. However, specific production was not significantly affected below 500 mOsm. But, at 500 mOsm, PTP1C production peak was shifted from 48 to 72 hpi. Because of the cell loss, this per cell yield increase did not translate into higher volumetric production. When glucose concentrations were kept at 5 mM by fed-batch addition, lactate production and increases in osmolarity were reduced. In shake flasks, this method permitted maximum production with cells resuspended either in fresh or spent medium at infection. This fed-batch process was implemented successfully at the 3.5-L scale. Fed-batch with glucose may provide a means to increase infected-cell density beyond 3×10^6 cells/mL.

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7380 239

S3 0 BIOREACTOR? AND 239

? s bioreactor? and 293

5004 BIOREACTOR?

7830 293

S4 6 BIOREACTOR? AND 293

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4/7/1 (Item 1 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

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07331243 91214772

A two-compartment cell entrapment bioreactor with three different holding times for cells, high and low molecular weight compounds.

Scholz M; Hu WS

Orthopedic Products Division, 3M Center, St. Paul, MN 55144-1000.

Cytotechnology (NETHERLANDS) Sep 1990, 4 (2) p127-37. ISSN 0920-9069

Journal Code: AT5

Languages: ENGLISH

Document type: JOURNAL ARTICLE

A new bioreactor for animal cell cultivation employs two compartments for cells and medium respectively. The two chambers are separated by an ultrafiltration membrane. Cells and solution of collagen or collagen/chitosan mixture were loaded to the cell chamber and were allowed to form gel inside. Contraction of the cell-laden gel occurred subsequently

to create a new zone in the cell chamber. In such a bioreactor cells are retained in the reactor, the high molecular product(s) accumulate in the cell chamber, while the small molecular weight nutrients and metabolites are replenished and removed from the medium chamber. By adjusting the flow rates for cell and medium chambers, the resident time for cells, high and low molecular weight components of the system can be manipulated separately. The new bioreactor, in both flat-bed and hollow-fiber configurations, was used to cultivate recombinant human cell, 293, for Protein C production over 60 to 90 days.

\$3.80 2 Type(s) in Format 7
 \$3.80 28 Types
 \$8.90 Estimated cost File73
 OneSearch, 2 files, 1.000 DialUnits FileOS
 \$10.33 Estimated cost this search
 \$43.43 Estimated total session cost 6.043 DialUnits
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4/7/5 (Item 4 from file: 73)
 DIALOG(R)File 73:EMBASE
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 8716622 EMBASE No: 93020407

Cultivation of mammalian cells as aggregates in bioreactors: Effect of calcium concentration on spatial distribution of viability
 Peshwa M.V., Kyung Y.-S., McClure D.B., Hu W.-S.
 Dept. of Chem. Engin./Materials Sci., University of Minnesota,
 Minneapolis, MN 55455 USA
 BIOTECHNOL. BIOENG. (USA), 1993, 41/2 (179-187)
 CODEN: BIBIA ISSN: 0006-3592 ADONIS ORDER NUMBER:
 000635929300002W

5A164, B5

Not used

LANGUAGES: English SUMMARY LANGUAGES: English
 Recombinant human kidney epithelial 293 cells were cultivated as aggregates in suspension. The concentration of calcium ion, in the range of 100 microm to 1 mM, affected the rate of aggregate formation. During the course of cultivation the size distribution of aggregates shifted and the fraction of larger aggregates increased. This effect was more profound in cultures with a high calcium concentration. Scanning and transmission microscopic examination of the aggregates revealed that cell packing was greater in the high calcium cultures and that ultrastructural integrity was retained in aggregates from both low and high calcium cultures. Confocal microscopy was applied to examine the viability of cells in the interior of the aggregates. High viability was observed in the aggregates obtained from exponentially growing cultures. Aggregates from the high calcium culture in the stationary phase exhibited a lower viability in the interior. With its ease of retention in a perfusion bioreactor, aggregate cultures offer an alternative choice for large-scale operations.

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 \$0.40 2 Type(s) in Format 7
 \$0.40 23 Types
 \$1.43 Estimated cost File155
 \$5.10 0.658 DialUnits File73
 \$0.00 26 Type(s) in Format 6

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L1      1 BENZONASE OR PULMOZYME
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CN ***Nuclease, endo-, benzonase (9CI)*** (CA INDEX NAME)
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CN Benzon nuclease
CN ***Benzonase***
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CI MAN
SR CA
LC STN Files: AGRICOLA, BIOBUSINESS, BIOSIS, CA, CAPLUS, CIN, PNI,
RTECS*, TOXLIT, USPATFULL
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10 REFERENCES IN FILE CA (1967 TO DATE)
10 REFERENCES IN FILE CAPLUS (1967 TO DATE)
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"HELP COMMANDS" at an arrow prompt (=>).
=> file ca
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                                ENTRY  SESSION
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This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> s II
L2      10 L1
ENTER DISPLAY FORMAT (BIB): bib abs
L2 ANSWER 1 OF 10 CA COPYRIGHT 1998 ACS
AN 129:24991 CA
TI Genetic engineering, production and characterization of monomeric
variants of the dimeric Serratia marcescens endonuclease
AU Franke, Ingo; Meiss, Gregor; Blecher, Dinah; Gimadudinow, Oleg;
Urbanke, Claus; Pingoud, Alfred
CS Fachbereich Biologie, Institut für Biochemie, Justus-Liebig
Universität, Giessen, D-35392, Germany
SO FEBS Lett. (1998), 425(3), 517-522
CODEN: FEBLAL; ISSN: 0014-5793
PB Elsevier Science B. V.
DT Journal
LA English
AB The Serratia nuclease (Benzonase) is a non-specific endonuclease
which cleaves single- and double-stranded RNA and DNA. It is a
member of a large family of related endonucleases, most of which are
dimers of identical subunits, with the notable exception of the
Anabaena nuclease which is a monomer. In order to find out whether
the dimer state of the Serratia nuclease is essential for its
function we have produced variants of this nuclease which based on
the crystal structure (Miller, M.D. and Krause, K.L. (1996), Protein
Science 5, 24-33) were expected to be unable to dimerize. We
demonstrate here that these variants, H184A, H184N, H184T and H184R,
are monomers and have the same secondary structure, stability toward
chem. denaturation and activity as the wild-type enzyme. This
allows one to conclude that the dimeric state is not essential for
the catalytic function of the Serratia nuclease. In contrast, the
S179C variant which is also a monomer shows little activity,
presumably because this amino acid substitution changes the
structure of the enzyme.
L2 ANSWER 2 OF 10 CA COPYRIGHT 1998 ACS
AN 126:261205 CA
TI Ultrasound permeabilizes CHO cells for the endonucleases AluI and
benzon nuclease
AU Johannes, Christian; Obe, Guenter
CS University of Essen, Department of Genetics, P. O. Box 45037, Essen,

```

D-45117, Germany

SO Mutat. Res. (1997), 374(2), 245-251

CODEN: MUREAV; ISSN: 0027-5107

PB Elsevier

DT Journal

LA English

AB Ultrasound permeabilizes Chinese hamster ovary (CHO) cells for the endonucleases Abul and benzon nuclease which leads to the induction of chromosomal aberrations by these enzymes. A few aberrant cells were obsd. when trypsinized cells or adherent cells were exposed to the enzymes in the absence of ultrasound. Our data show that sonication can be used to introduce endonucleases into CHO cells. We further demonstrate that few cells can internalize endonucleases without previous permeabilization.

L2 ANSWER 3 OF 10 CA COPYRIGHT 1998 ACS

AN 125:240235 CA

TI Endonuclease digestion followed by chromatography in method of purification of recombinant viral vectors containing a therapeutic gene

IN Shabram, Paul W.; Huyghe, Bernard G.; Liu, Xiaodong; Shepard, H. Michael

PA Camj, Inc., USA

SO PCT Int. Appl., 40 pp.
CODEN: PLYXD2

P1 WO 96/27677 A2 960912

DS W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI

RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, NL, PT, SE

AI WO 96-US3369 960306

PRAI US 95-400793 950307

DT Patent

LA English

AB The invention provides a method for purifying viral vectors contg. therapeutic genes for use in gene therapy. The invention comprises a method of purifn. from a cell lysate of a recombinant viral vector contg. a therapeutic gene which comprises: (a) treating said lysate with an enzymic agent that selectively degrades both unencapsulated DNA and RNA; (b) chromatographing the treated lysate from step (a) on a first resin; and (c) chromatographing the eluant from step (b) on a second resin; wherein one resin is an anion exchange resin and the other is an immobilized metal ion chromatog. (IMAC) resin or a hydrophobic interaction chromatog. resin.

L2 ANSWER 4 OF 10 CA COPYRIGHT 1998 ACS

AN 123:309251 CA

TI Sequence preferences in cleavage of dsDNA and ssDNA by the extracellular Serratia marcescens endonuclease

AU Meiss, Gregor; Friedhoff, Peter; Hahn, Meinhard; Gimadudinow, Oleg; Pingoud, Alfred

CS Institut fuer Biochemie, Justus-Liebig-Universitaet, Giessen,

D-35392, Germany

SO Biochemistry (1995), 34(37), 11979-88

CODEN: BICHAW; ISSN: 0006-2960

DT Journal

LA English

OS CIACS-IMAGE; CIACS

AB The preferred cleavage sites in dsDNA and ssDNA for the extracellular Serratia marcescens endonuclease (corn. available as BENZONASE) were identified by limited digestion of PCR-generated substrates. Two different dsDNA substrates were synthesized by using either radioactively or fluorescent dye labeled primers. ssDNA of identical sequence to one of the fluorescent dye labeled duplex strands was prepd. by affinity chromatog. Cleavage exps. carried out under single hit conditions demonstrate that the enzyme shows preferences for GC-rich regions in dsDNA, in particular d(G).cndot.d(C)-tracts, and avoids cleavage of d(A).cndot.d(T)-tracts. There is a correlation between cleavage at a given position in one strand with cleavage at the same position in the other strand of the duplex. ssDNA cleavage occurs at somewhat different preferred sites than obsd. in dsDNA. On dsDNA, the Serratia nuclease produces a very different cleavage pattern compared to bovine pancreatic DNase I, with the notable exception that both enzymes avoid d(A).cndot.d(T)-tracts. In general, the Serratia nuclease compared to DNase I is a slightly more nonspecific endonuclease that attacks a particular substrate more evenly under std. reaction conditions. At high ionic strength or in the presence of DMSO, it becomes more nonspecific. Addn. of urea, however, makes the enzyme more selective than obsd. under std. conditions. From these results which were confirmed by the results of cleavage exps. with synthetic oligodeoxynucleotides, we conclude that the Serratia nuclease like DNase I is sensitive to global features of the DNA, for example, the width of the minor groove. In addn., localized sequence-dependent interactions between substrate and nuclease det. whether a site is cleaved preferentially. Some of these interactions seem to be the same for ds- and ssDNA.

L2 ANSWER 5 OF 10 CA COPYRIGHT 1998 ACS

AN 122:125450 CA

TI A new mass spectrometric approach to detect modifications in DNA
AU Janning, Petra; Schrader, Wolfgang; Linscheid, Michael

- CS Inst. Spektrochim. Angew. Spektroskopie, Dortmund, D-44013, Germany
 SO Rapid Commun. Mass Spectrom. (1994), 8(12), 1035-40
 CODEN: RCMSEF; ISSN: 0951-4198
 DT Journal
 LA English
- AB A new approach is described for the enzymic digestion of DNA yielding oligonucleotides ranging from dinucleoside monophosphates to octanucleoside heptaphosphates. DNA was digested by means of the benzon nuclease, as unspecific nuclease, and alk. phosphatase to remove the terminal phosphate. The mixt. of oligonucleotides was sepd. using capillary-zone electrophoresis with a buffer system, yielding a rather strong electroosmotic flow. The oligomers are sepd. into groups with nucleotides of the same chain length. The sepn. capillary was used as the innermost capillary of an electrospray spraying system. Neg. mol. ions of the nucleotides were recorded using a home-built interface and ion source for a sector-field mass spectrometer. This approach allows the facile detection of DNA modifications since they lead not only to differences in mass, but also can possess altered electrophoretic mobility. For modifying reactions which exhibit sequence specificity, the information is retained in the oligomers. Thus, reactions of DNA with electrophiles can be evaluated at different levels, since in longer chains, even complex sequence specificity may be apparent. Results from calf thymus DNA digests and preliminary expts. with DNA adducts with styrene oxide are discussed.
- L2 ANSWER 6 OF 10 CA COPYRIGHT 1998 ACS
 AN 122:99113 CA
 TI Induction of chromosomal aberrations with benzon nuclease in Chinese hamster ovary (CHO) cells
 AU Johannes, C.; Obe, G.
 CS University GH Essen, Department of Genetics, P.O. Box 45037, Essen, D-45117, Germany
 SO Mutat. Res. (1994), 325(2/3), 113-16
 CODEN: MUREAV; ISSN: 0027-5107
 DT Journal
 LA English
- AB Benzon nuclease, an endonuclease originating from *Serratia marcescens*, was tested for its chromosome-breaking activity in Chinese hamster ovary cells. Using a permeabilizing method with hypertonic glycerol, benzon nuclease induced chromosomal aberrations in an S-phase independent manner. The frequencies of polycentric chromosomes were correlated with the dose of the enzyme and the intercellular distribution of aberrations was overdispersed.
- L2 ANSWER 7 OF 10 CA COPYRIGHT 1998 ACS
- AN 121:127519 CA
 TI Induction of sister-chromatid exchanges by AluI, DNase I, benzon nuclease and bleomycin in Chinese hamster ovary (CHO) cells
 AU Obe, G.; Schunck, C.; Johannes, C.
 CS University GH Essen, Department of Genetics, P.O. Box 45037, D-45117, Essen, Germany
 SO Mutat. Res. (1994), 307(1), 315-21
 CODEN: MUREAV; ISSN: 0027-5107
 DT Journal
 LA English
- AB Various endonucleases (AluI, DNase I, benzon nuclease) and bleomycin induce sister-chromatid exchanges (SCE) in Chinese hamster ovary (CHO) cells. The frequencies of SCE are elevated in cells with chromosome-type aberrations, only slightly elevated in cells with chromatid exchanges, and in the control range in cells without chromosomal aberrations. These data indicate that SCE are produced when DNA breaks induced in G1 are either not repaired or misrepaired.
- L2 ANSWER 8 OF 10 CA COPYRIGHT 1998 ACS
 AN 120:72890 CA
 TI Activated polymeric carriers, their fabrication and use
 IN Mueller, Egbert, Badel, Kerstin, Mueller, Andreas, Herbert, Stefan; Seiler, Anja
 PA Merck Patent G.m.b.H., Germany
 SO Eur. Pat. Appl., 20 pp.
 CODEN: EPXXDW
 PI EP 565978 A1 931020
 DS R: AT, BE, CH, DE, FR, GB, IT, LI, NL
 AI EP 93-105560 930403
 PRAI DE 92-4212730 920416
 DT Patent
 LA German
- AB Activated linear polymers, attached to a hydroxylated carrier and bearing oxirane or azlactone groups, are prepd. which can be used for immobilization of enzymes or ligands for affinity chromatog. of biopolymers. The polymers are prepd. from monomers R1R2C:CR3Y (R1, R2, R3 = H, Me; Y = oxirane- or azlactone-conn. substituent) which may optionally be copolymd. with R1R2C:CR3C(O)NH2. Thus, poly(acryloyl-2-methylalanine) was grafted onto Fractogel-TSK HW 65 (S) using cerium(IV) ammonium nitrate as initiator and cyclized to an azlactone with Ac2O for immobilization of protein A.
- L2 ANSWER 9 OF 10 CA COPYRIGHT 1998 ACS
 AN 116:150344 CA
 TI Hydrolysis of nucleic acids in single-cell protein concentrates using immobilized benzonase

AU Moreno, J. M.; Sanchez-Montero, J. M.; Ballesteros, A.; Sinisterra, J. V.

CS Fac. Pharm., Univ. Complutense, Madrid, 28040, Spain

SO Appl. Biochem. Biotechnol. (1991), 31(1), 43-51

CODEN: ABIBDL; ISSN: 0273-2289

DT Journal

LA English

AB Hydrolysis of nucleic acids for single-cell protein concs. was carried out in 1 step by using benzonase immobilized on corncob particles. The immobilization was carried out by tosylation of primary alcs. of cellulose of corncob. The immobilized benzonase was more stable to pH changes than native benzonase, but the same optimum values of Mg concn. and temp. were obtained. The DNase activity was greater than the RNase activity. The protein DNA content was reduced to 3-6% and that of RNA to 50%. The protein loss was negligible (1%). The enzymic activity/unit wt. of enzyme was greater for benzonase than for other nucleases insolubilized on corncob by the same procedure.

L2 ANSWER 10 OF 10 CA COPYRIGHT 1998 ACS

AN 116:54600 CA

T1 Contribution to the study of the enzymatic activity of benzonase

AU Moreno, J. M.; Sanchez-Montero, J. M.; Sinisterra, J. V.; Nielsen, L. B.

CS Fac. Pharm., Univ. Complutense, Madrid, 28040, Spain

SO J. Mol. Catal. (1991), 69(3), 419-27

CODEN: JMCADS; ISSN: 0304-5102

DT Journal

LA English

AB The hydrolytic activity of benzonase has been studied at different values of Mg(II) concn., pH, temp. and percentages of water-miscible org. solvents (DMSO, THF, acetonitrile and DMF). The action of these parameters on the UV spectra of benzonase has been analyzed. The best exptl. conditions (pH = 8.0, T = 37.degree., [Mg(II)] = 2 mM) lead to a well-defined conformation. This conformation is active vs. DNA and RNA. Changes in these parameters give conformational alterations which can be monitored by changes in the UV spectra. Org. solvents deactivate the enzyme by hydrophobic interaction of the lipophilic solvent mols. with the aliph. residues of the protein. DMF, the most hydrophilic solvent tested, gives slight deactivation of the enzyme. Benzonase hydrolyzes native DNA, heat-denatured DNA and RNA. The active site seems to be the same in all cases. Benzonase has been immobilized for the first time, retaining high enzymic activity.

=> log hold

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? b 155
 20jul98 08:34:57 User208669 Session D1216.1
 \$0.20 0.062 DialUnits File1
 \$0.20 Estimated cost File1
 \$0.20 Estimated cost this search
 \$0.20 Estimated total session cost 0.062 DialUnits

File 155:MEDLINE(R) 1966-1998/Sep W2
 (c) format only 1998 Dialog Corporation
 *File 155: format of UD= has changed.

Set Items Description
 --- -----
 ? s pulmozyme
 S1 13 PULMOZYME
 ? ts17/1 9-13
 17/11

DIALOG(R)File 155:MEDLINE(R)
 (c) format only 1998 Dialog Corporation. All rts. reserv.
 08910244 97071275
 Stability characterization and formulation development of recombinant human deoxyribonuclease I [Pulmozyme, (dornase alpha)].
 Shire SI
 Department of Pharmaceutical Research and Development, Genentech, Inc., South San Francisco, California 94080, USA.
 Pharm Biotechnol (UNITED STATES) 1996, 9 p393-426, ISSN 1078-0467
 Journal Code: BYR
 Languages: ENGLISH
 Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL (84 Refs.)

17/9
 DIALOG(R)File 155:MEDLINE(R)
 (c) format only 1998 Dialog Corporation. All rts. reserv.
 08127706 95168583
 Colorimetric determination of DNase I activity with a DNA-methyl green substrate.
 Sinicropi D, Baker DL, Prince WS, Shifter K, Shak S
 Department of BioAnalytical Technology, Genentech, Inc., South San Francisco, California 94080.
 Anal Biochem (UNITED STATES) Nov 1 1994, 222 (2) p351-8, ISSN 0003-2697 Journal Code: 4NK
 Languages: ENGLISH
 Document type: JOURNAL ARTICLE
 A simple, high throughput, and precise assay was developed for quantification of deoxyribonuclease I (DNase; IUB 3.1.21.1) activity. The method was adapted from the procedure devised by Kunitz which employs a substrate comprised of highly polymerized native DNA complexed with methyl green. Hydrolysis of the DNA produced unbound methyl green and a decrease in the absorbance of the solution at 620 nm. By adjusting the time and temperature of the reaction, the assay permits quantification of DNase activity over a wide concentration range (0.4 to 8900 ng/ml). Samples and standards were added to the substrate in microtiter plates and were incubated for 1-24 h at 25-37 degrees C to achieve the desired assay range. The DNase activity of the samples was interpolated from a standard curve generated with Pulmozyme recombinant human deoxyribonuclease I (rhDNase). Interassay precision was less than 12% CV and recovery was within 100 +/- 11%. Activity determination by the DNA-methyl green method correlated well with that determined by the widely used "hyperchromicity" method originated by Kunitz, which is based on the increase in absorbance at 260 nm upon hydrolysis of DNA. The DNA-methyl green assay was simpler and more versatile than the hyperchromicity method and was used to characterize the activity of rhDNase and DNase isolated from human urine.

17/10
 DIALOG(R)File 155:MEDLINE(R)
 (c) format only 1998 Dialog Corporation. All rts. reserv.
 08002656 9437316
 Consensus conference: practical applications of Pulmozyme. September 22, 1993.
 Ramsey BW, Dorkin HL
 Cystic Fibrosis Center, Children's Hospital & Medical Center, Seattle, WA 98105.
 Pediatr Pulmonol (UNITED STATES) Jun 1994, 17 (6) p404-8, ISSN 8755-6863 Journal Code: OWH
 Languages: ENGLISH
 Document type: CONSENSUS DEVELOPMENT CONFERENCE; JOURNAL ARTICLE; REVIEW (8 Refs.)

17/11
 DIALOG(R)File 155:MEDLINE(R)
 (c) format only 1998 Dialog Corporation. All rts. reserv.
 07955618 94304663
 Pharmacologic expert report Pulmozyme rhDNase Genentech, Inc.
 Green JD
 Genentech, Inc., South San Francisco, California.
 Hum Exp Toxicol (ENGLAND) May 1994, 13 Suppl 1 pS1-42, ISSN 0960-3271
 Journal Code: AOL
 Languages: ENGLISH
 Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC (48 Refs.)

17/12

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

07948810 94295212

[Pulmozyme (Dornase alfa)]

Pulmozyme (Dornase Alfa).

Togthofer W

Wien Klin Wochenschr (AUSTRIA) 1994, 106 (8) p253-6, ISSN 0043-5325

Journal Code: XOP

Languages: GERMAN

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

(13 Refs.)

1/7/13

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

07937152 94277676

Pulmozyme--Dornase alfa.

Gutteridge C, Kuhn RJ

Pediatr Nurs (UNITED STATES) May-Jun 1994, 20 (3) p278-9, ISSN

0097-9805 Journal Code: OUN

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Dornase alfa is the first new drug released in 30 years for the treatment of patients with CF. Although it does not represent a replacement for current standard therapies, it is an effective agent in improving lung function. The development of this drug has helped to provide treatment to a medical problem that physicians have struggled with treating for years.

? log hold

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\$1.20 6 Type(s) in Format 7

\$1.20 19 Types

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\$4.20 Estimated cost this search

\$4.40 Estimated total session cost 1.062 DialUnits

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Reconnected in file 155 20jul98 08:53:27

File 155:MEDLINE(R) 1966-1998/Sep W2

(c) format only 1998 Dialog Corporation

*File 155: format of UD= has changed.

Set Items Description

? s au=moshet, m?

S2 0 AU=MOSHER, M?

? e au=mosher m?

Ref Items Index-term

E1 39 AU=MOSHER LR

E2 9 AU=MOSHER M

E3 0 *AU=MOSHER M?

E4 12 AU=MOSHER MB

E5 5 AU=MOSHER MD

E6 8 AU=MOSHER ME

E7 1 AU=MOSHER MF

E8 1 AU=MOSHER ML JR

E9 3 AU=MOSHER MR

E10 1 AU=MOSHER N

E11 2 AU=MOSHER NL

E12 1 AU=MOSHER P

Enter P or PAGE for more

? s e2,e4

9 AU=MOSHER M

12 AU=MOSHER MB

S3 21 E2,E4

? t s4/3/1 2 4-8

4/3/1

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

06239240 85182594

H+-ATPase of Escherichia coli. An uncl. mutation impairing coupling between F1 and Fo but not Fo-mediated H⁺ translocation.

Moshet ME; White LK; Hermolin J; Fillingame RH

J Biol Chem (UNITED STATES) Apr 25 1985, 260 (8) p4807-14, ISSN

0021-9258 Journal Code: HIV

Contract/Grant No.: GM-23105, GM, NIGMS; 5 T32 GM07215, GM, NIGMS

Languages: ENGLISH

Document type: JOURNAL ARTICLE

4/3/2

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

05523224 90173860

Use of lambda-unc transducing phages in genetic analysis of H(+)-ATPase mutants of Escherichia coli.

Fillingame RH; Mosher ME

Methods Enzymol (UNITED STATES) 1986, 126 p558-68, ISSN 0076-6879

Journal Code: MVA

Contract/Grant No.: GM-23105, GM, NIGMS

Languages: ENGLISH

Document type: JOURNAL ARTICLE

4/3/4

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

04491700 81069901

Subunits of the H⁺-ATPase of Escherichia coli. Overproduction of an eight-subunit F1F0-ATPase following induction of a lambda-transducing phage carrying the unc operon.

Foster DL; Mosher ME; Futai M; Fillingame RH

J Biol Chem (UNITED STATES) Dec 25 1980, 255 (24) p12037-41, ISSN

0021-9258 Journal Code: HIV

Contract/Grant No.: GM023105, GM, NIGMS; GM-7215, GM, NIGMS; 5 T32

GM07215, GM, NIGMS

Languages: ENGLISH

Document type: JOURNAL ARTICLE

4/3/5

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

04427459 84289384

A phenylalanine for serine substitution in the beta subunit of Escherichia coli F1-ATPase affects dependence of its activity on divalent cations.

Noumi T; Mosher ME; Natori S; Futai M; Kanazawa H

J Biol Chem (UNITED STATES) Aug 25 1984, 259 (16) p10071-5, ISSN

0021-9258 Journal Code: HIV

Contract/Grant No.: GM-23105, GM, NIGMS

Languages: ENGLISH

Document type: JOURNAL ARTICLE

4/3/6

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

04421796 84212269

Mutations altering aspartyl-61 of the omega subunit (uncE protein) of Escherichia coli H⁺-ATPase differ in effect on coupled ATP hydrolysis.

Fillingame RH; Peters LK; White LK; Mosher ME; Paule CR

J Bacteriol (UNITED STATES) Jun 1984, 158 (3) p1078-83, ISSN

0021-9193 Journal Code: HH3

Contract/Grant No.: GM23105, GM, NIGMS; 5 T32 GM07215, GM, NIGMS

Languages: ENGLISH

Document type: JOURNAL ARTICLE

4/3/7

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

04332365 84061611

Use of lambda unc transducing bacteriophages in genetic and biochemical characterization of H⁺-ATPase mutants of *Escherichia coli*.

Mosher ME; Peters LK; Fillingame RH

J Bacteriol (UNITED STATES) Dec 1983, 156 (3) p1078-92, ISSN

0021-9193 Journal Code: HH3

Contract/Grant No.: GM-23105, GM, NIGMS; 5 T32 GM07215, GM, NIGMS

Languages: ENGLISH

Document type: JOURNAL ARTICLE

4/3/8

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

04323035 83082929

H⁺-ATPase of *Escherichia coli* uncB402 mutation leads to loss of chi subunit of subunit of F0 sector.

Fillingame RH; Mosher ME; Negria RS; Peters LK

J Biol Chem (UNITED STATES) Jan 10 1983, 258 (1) p604-9, ISSN

0021-9258 Journal Code: HHV

Contract/Grant No.: GM-23105, GM, NIGMS; 5 T32 GM07215, GM, NIGMS

Languages: ENGLISH

Document type: JOURNAL ARTICLE

? log hold

20jul98 08:56:26 User208669 Session D1216.3

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\$0.00 29 Type(s) in Format 6

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\$4.40 Estimated cost this search

\$4.40 Estimated total session cost 1.000 DialUnits

Logoff: level 98.07.06 D 08:56:26

Reconnected in file 155 20jul98 09:23:29

File 155:MEDLINE(R) 1966-1998/Sep W2

(c) format only 1998 Dialog Corporation

*File 155: format of UD= has changed.

Set Items Description

? s diafiltration

S5 95 DIAFILTRATION

? t s57/28

5/7/28

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

05921921 88251541

Purification of proteins produced by biotechnological process.

Werner RG; Berthold W

Dr. Karl Thoma GmbH, Bioengineering Techniques, Biberach an der Riss,

Fed. Rep. of Germany.

Arzneimittelforschung (GERMANY, WEST) Mar 1988, 38 (3) p422-8, ISSN

0004-4172 Journal Code: 91U

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

Proteins maintain functions important to life. Faulty functioning or deficiency gives rise to pathological reactions. These proteins can now be produced, using the methods of recombinant DNA technology and administered to patients for replacement therapy. Many proteins as active ingredients are already available for use as immunomodulators, agents for tumour treatment, plasma proteins and hormones. They are in various stages of development, ranging from cloning of the producing cells to marketing of the finished products. Since the active substances are proteins synthesized by recombinant cells, their purification presents a particular challenge to protein chemists. Purification of recombinant DNA-derived proteins intended for human use is an essential part of the biotechnical process. It starts immediately after the fermentation of the host cell. The characteristics of the protein determine which microorganisms or cell cultures are used and this in turn defines the first purification step. The microorganisms are disrupted, and the insoluble protein, deposited in "inclusion bodies" has to be renatured, or the proteins secreted by cells and have to be concentrated. The subsequent strategy for purification of the protein does not depend on the fermentation process but is entirely determined by the physicochemical properties of the proteins. The goal of the first purification step is to isolate as fast and quantitatively as possible the recombinant protein from the culture filtrate, in order to minimize potential changes brought about by proteases or glycosidases. Immunoaffinity or ligand-affinity chromatography is used preferentially for this purpose. The concentration of protein and buffer changes are carried out by precipitation followed by reconstitution or, preferably, by dialysis and ultrafiltration/diafiltration (ABSTRACT TRUNCATED AT 250 WORDS) (32 Refs.)

? b 357

20jul98 09:27:53 User208669 Session D1216.4

\$3.00 1.000 DialUnits File155

\$0.00 95 Type(s) in Format 6
\$0.20 1 Type(s) in Format 7
\$0.20 96 Types
\$3.20 Estimated cost File155
\$3.20 Estimated cost this search
\$3.20 Estimated total session cost 1.000 DialUnits

File 357:Derwent Biotechnology Abs 1982-1998/Aug B1
(c) 1998 Derwent Publ Ltd

Set Items Description

? s diafiltration

S1 219 DIAFILTRATION

? s virus

S2 22249 VIRUS

? s s1 and s2

219 S1

22249 S2

S3 26 S1 AND S2

? t s3/7/2 3 6 17 25

3/7/2

DIALOG(R)File 357:Derwent Biotechnology Abs

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199674 DBA Accession No.: 96-09854 PATENT

Isolation of recombinant hepatitis B virus surface antigen - purification by chaotropic salt, surfactant and alkali extraction, followed by chromatography, for use as a recombinant vaccine

AUTHOR: Park S J, Lee Y M, Yoon K H, Lim K J, Kwon Y S

CORPORATE SOURCE: Seoul, Korea.

PATENT ASSIGNEE: LG-Chem. 1996

PATENT NUMBER: EP 716094 PATENT DATE: 960612 WPI ACCESSION NO.: 96-269949

(9628)

PRIORITY APPLIC. NO.: KR 33594 APPLIC. DATE: 941210

NATIONAL APPLIC. NO.: EP 95119383 APPLIC. DATE: 951208

LANGUAGE: English

ABSTRACT: A new process for purification of a recombinant hepatitis B virus surface antigen pre-S2 peptide involves cell disintegration in buffer with a chaotropic salt (1-8 M sodium thiocyanate, potassium thiocyanate, ammonium thiocyanate, guanidinium chloride or urea) to obtain a cell homogenate. Surfactant (0.1-0.5% w/v Tween-20, Tween-80, Triton X-100 or sodium deoxycholate) may be added, followed by alkali extraction (pH to 11.0-13.5), silica gel chromatography (at pH 4.5-6.0, with silica surface area 100-500 sq m/g and elution at pH 8.8-11.0 with 1-8 M urea and 0.1-0.3 wt% surfactant), hydrophobic interaction chromatography on phenyl-agarose (at pH 8.8-11.0 with 1-4 M urea, washed with 10-40 wt.% ethylene glycol (EG), and eluted with 60-80 wt.% EG), and gel filtration on dextran or polyacrylamide gel with a mol. wt. cutoff of at least 1,000,000 (in Tris or phosphate buffer, pH 6-8, with 0.1-0.2 M NaCl). A salt may be added at the surfactant and/or alkali extraction steps, and chromatography may be preceded by removal of cell debris and contaminants and diafiltration. The antigen may be used as a

recombinant vaccine. (12pp)

3/7/3

DIALOG(R)File 357:Derwent Biotechnology Abs

(c) 1998 Derwent Publ Ltd. All rts. reserv.

194906 DBA Accession No.: 96-05677 PATENT

Pure influenza antigen preparation by ultrafiltration of viral suspension - influenza virus antigen purification; useful in vaccine and as diagnostic reagents

AUTHOR: Violay J M, Court G, Gerdil C, Chalumeau H, McVerry P

CORPORATE SOURCE: Lyon, France.

PATENT ASSIGNEE: Pasteur-Merieux-Serums-Vaccines 1996

PATENT NUMBER: WO 9605294 PATENT DATE: 960222 WPI ACCESSION NO.: 96-139692 (9614)

PRIORITY APPLIC. NO.: FR 9410039 APPLIC. DATE: 940816

NATIONAL APPLIC. NO.: WO 95US727 APPLIC. DATE: 950606

LANGUAGE: French

ABSTRACT: Preparation of purified influenza virus (IV) antigens (A) from a liquid containing IV comprises (a) purification by ultracentrifugation, filtration step, and/or (b) fragmentation of live virus in the presence of an amphiphilic, nonionic surfactant (I) then elimination of undesirable components before filtration that retains all the viral components. If both steps (a) and (b) are used, they may be done in either order. (I) is preferably octoxynol-9 (Triton X-100). In a preferred process, comprising step (a) only or steps (a) and (b), the virus composition is particularly purified by zonal centrifugation, especially in a sucrose gradient at about 9,000 x g, then filtered (down to a minimum pore size of 0.3 um) and ultracentrifugation repeated. The resulting viral suspension is standardized (to a protein concentration of 0.2-1 ng/ml) using buffer (phosphate-buffered saline) and fragmented at 20-25 deg by the addition of (I). Undesirable components are removed by diafiltration. The starting material is particularly allantoic fluid from embryonated eggs being used to cultivate the virus. (A) are used to make IV vaccines or diagnostic reagents. (17pp)

3/7/6

DIALOG(R)File 357:Derwent Biotechnology Abs

(c) 1998 Derwent Publ Ltd. All rts. reserv.

161874 DBA Accession No.: 94-04425 PATENT

Production of hepatitis A virus vaccine - in MRC-5 cell culture on a titanium or stainless steel mesh carrier in a static surface culture vessel, and purification by cell permeabilization, nuclease treatment and chromatography

PATENT ASSIGNEE: Merck-USA 1994

PATENT NUMBER: EP 583142 PATENT DATE: 940216 WPI ACCESSION NO.: 94-050440

biological materials. (8 ref)

3/7/25
DIALOG(R)File 357:Derwent Biotechnology Abs

(c) 1998 Derwent Publ Ltd. All rts. reserv.

038151 DBA Accession No.: 85-08940 PATENT
Filtration of biological solutions - useful in the purification of e.g.
influenza virus

PATENT ASSIGNEE: Res-Inst.Pure-Biol.Prep. 1984

PATENT NUMBER: SU 1126308 PATENT DATE: 841130 WPI ACCESSION NO.:
85-151317 (8525)

PRIORITY APPLIC. NO.: SU 3550117 APPLIC. DATE: 821202
NATIONAL APPLIC. NO.: SU 3550117 APPLIC. DATE: 821202
LANGUAGE: Russian

ABSTRACT: Biological solutions can be purified by diafiltration in a
process involving washing the solution with a solvent under pressure
impulses of 0.1-20 sec duration at intervals of 0.05-0.2 m/sec over a
membrane surface. Preferably, the pressure impulses are about 0.05 MPa.
This process has high productivity. In an example, a biological
solution containing A2/Hong Kong influenza virus at a titer of 1.8192
(hemagglutination) and containing 4.65 mg/ml of protein was diafiltered
using 0.5 M tris-HCl buffer. Pulses of 0.033 MPa lasting 10 sec were
applied at a period of 10 sec and the solution was moved over the
membrane surface at 0.05 m/sec. The productivity of the process was 32
l/hr/sq cm. The same volume of solution was recovered, having a virus
titer of 1.8192 and containing 0.130 mg/ml protein. (8pp)

? s dia(w)filtration
39 DIA

8665 FILTRATION

S4 4 DIA(W)FILTRATION

? s cross(w)flow

4534 CROSS

9109 FLOW

S5 446 CROSS(W)FLOW

? ds

Set Items Description

S1 219 DIAFILTRATION

S2 22249 VIRUS

S3 26 S1 AND S2

S4 4 DIA(W)FILTRATION

S5 446 CROSS(W)FLOW

? s s2 and s5

22249 S2

446 S5

S6 12 S2 AND S5
? ds

(9407)

PRIORITY APPLIC. NO.: US 926873 APPLIC. DATE: 920810

NATIONAL APPLIC. NO.: EP 93306223 APPLIC. DATE: 930806
LANGUAGE: English

ABSTRACT: A commercial-scale process for production of hepatitis A virus
(HAV) of greater than 95% purity with respect to protein by SDS-PAGE
and silver stain analysis comprises: culturing HAV in large quantities
in MRC-5 cell sheets in a large-surface-area static surface culture
vessel (SSCV); surfactant (e.g. 0.05-1% Triton X-100) cell
permeabilization of infected cells to liberate HAV; optionally removing
non-HAV-specific nucleic acids by nuclease (e.g. Benzonase) treatment;
concentrating HAV by membrane diafiltration or ionexchange capture;
removing non-HAV proteins by organic solvent extraction, PEG
precipitation, anion-exchange chromatography on DEAE-Toyopearl 650M and
gel filtration on Toyopearl; recovering purified HAV; and inactivating
by formaldehyde treatment. In the vessel, the culture medium is
constantly circulated, and contains a loop for systems control,
aeration and replenishment of culture components. An inactivated HAV
vaccine is produced as above, or in a Nunc cell factory or Costar cube.
The SSCV has a regular mesh element carrier (titanium or stainless
steel gauze) for high cell density culture. (71pp)

3/7/17

DIALOG(R)File 357:Derwent Biotechnology Abs

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096117 DBA Accession No.: 89-14108

Equipment design of biological liquids separation by means of
ultrafiltration on hole fibers - diafiltration, concentration,
purification

AUTHOR: Petrov S V; Zenkevich V B; Sakulina L M

CORPORATE SOURCE: Pilot-scale Design Bureaux of Fine Biological
Engineering, Kirishi, Leningrad Region, USSR.

JOURNAL: Biokhimiya (5, 4, 485-91) 1989

CODEN: BTKNEZ

LANGUAGE: Russian

ABSTRACT: The design of equipment for the separation of biological fluids
by ultrafiltration on hole fibers is discussed. Fiber VPU-15PA based on
an aromatic polyamide (phenilon S-2) was used. Schematic
representations of devices for batch and continuous concentration of
solutions and for diafiltration are presented. Features and limitations
of devices based on hole fibers are considered. Reference is made to
the use of hole fibers for concentration of influenza virus suspensions
in allantoic fluid during the production of inactivated influenza
vaccine, purification of hydroxyethyl starch by diafiltration, protein
concentration, and removal of cell fragments from baker's yeast
(*Saccharomyces cerevisiae*) autolyzate. The equipment described may be
used for concentration, purification, and isolation of a wide range of

useful for gene therapy. (12pp)
 ? ds

Set Items Description
 S1 219 DIAFILTRATION
 S2 22249 VIRUS
 S3 26 S1 AND S2
 S4 4 DIA(W)FILTRATION
 S5 446 CROSS(W)FLOW
 S6 12 S2 AND S5
 S7 33 DIAFLT? NOT S1
 S8 2 S7 AND S2
 ? s viruses not s2
 3884 VIRUSES

22249 S2
 S9 488 VIRUSES NOT S2
 ? s s9 and (s1 or s4 or s5 or s7)
 488 S9

219 S1
 4 S4
 446 S5
 33 S7
 S10 2 S9 AND (S1 OR S4 OR S5 OR S7)
 ? t s10/7/2

10/7/2

DIALOG(R)File 357:Derwent Biotechnology Abs

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032884 DBA Accession No.: 85-03673

Cell separations with hollow fiber membranes - application to plant and animal cell culture etc. (conference paper)

AUTHOR: Tutunjian R S
 CORPORATE AFFILIATE: Amicon
 CORPORATE SOURCE: Amicon Corporation, 17 Cherry Hill Drive, Danvers, Massachusetts 01923, U.S.A.
 JOURNAL: Dev.Ind.Microbiol. (25, 415-35) 1984
 CODEN: DIMCAL

LANGUAGE: English

ABSTRACT: The use of hollow-fiber filters for processing cells has become an important part of biotechnology and membranes have been used to harvest and wash bacteria as well as recover extracellular products. Hollow fibers have been used in place of continuous centrifuges. Utilizing cross-flow filtration techniques, final cell densities of over 90% (v/v) or 260 g/l have been achieved. Optimal performance generally requires high flow rates across the filter surface. Continuous fermentation with cell recycle also has been performed using hollow fibers. Extracellular products and inhibitory by-products may be

Set Items Description
 S1 219 DIAFILTRATION
 S2 22249 VIRUS
 S3 26 S1 AND S2
 S4 4 DIA(W)FILTRATION
 S5 446 CROSS(W)FLOW
 S6 12 S2 AND S5
 ? s diaflt? not s1
 252 DIAFLT?

219 S1
 S7 33 DIAFLT? NOT S1
 ? s s7 and s2

33 S7
 22249 S2
 S8 2 S7 AND S2
 ? t s8/7/1

8/7/1

DIALOG(R)File 357:Derwent Biotechnology Abs

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216633 DBA Accession No.: 97-11754 PATENT

Purification of retro viral vector from culture supernatant of producer cells - retro virus vector purification by ionexchange chromatography

for use in gene therapy

AUTHOR: Kotani H; Newton III P; Zhang S

CORPORATE SOURCE: Gaithersburg, MD, USA.

PATENT ASSIGNEE: Genet. Ther. 1997

PATENT NUMBER: US 5661022 PATENT DATE: 970826 WPI ACCESSION NO.: 97-434382 (9740)

PRIORITY APPLIC. NO.: US 468826 APPLIC. DATE: 950606

NATIONAL APPLIC. NO.: US 468826 APPLIC. DATE: 950606

LANGUAGE: English

ABSTRACT: A new method for purifying infectious retro virus vector particles to obtain a purified retro virus supernatant containing

infectious retro virus particles involves: generating retro virus vector particles by culturing retro virus vector producer cells; obtaining a supernatant containing the retro virus vector particles from the culture of retro virus vector producer cells; concentrating the supernatant, preferably by tangential flow filtration; diafiltering the supernatant, subjecting the supernatant to ionexchange chromatography on a resin with trialkylammonium groups, especially trimethylammonioethyl or triethylammonioethyl groups; concentrating the supernatant; diafiltering the supernatant to give a purified retro virus supernatant containing infectious retro virus particles; optionally also lyophilizing the infectious retro virus vector particles; and optionally reconstituting the retro virus vector particles The purification factor is as high as 40. The vectors are

removed while cell growth is maintained. Increased cell densities and productivity have been achieved for such products as ethanol and lactic acid. This technique should have increased impact as genetic research allows more products to be excreted. Large-scale culture of animal or plant cells also has been performed with hollow-fiber membranes. Cells grow continuously for weeks on the outside of the fibers to give high cell densities. Hollow fibers have been used to produce monoclonal antibodies, interferon, viruses, and other products. (25 ref)

?log hold

20jul98 09:37:57 User208669 Session D1216.5

\$10.50 2.000 DialUnits File357

\$0.00 46 Type(s) in Format 6

\$14.00 7 Type(s) in Format 7

\$14.00 53 Types

\$24.50 Estimated cost File357

\$24.50 Estimated cost this search

\$27.70 Estimated total session cost 3.000 DialUnits

Logoff: level 98.07.06 D 09:37:57

? b 155

20Jul98 12:21:30 User208669 Session D1217.1

\$0.16 0.049 DialUnits File1

\$0.16 Estimated cost File1

\$0.16 Estimated cost this search

\$0.16 Estimated total session cost 0.049 DialUnits

File 155:MEDLINE(R) 1966-1998/Sep W2

(c) format only 1998 Dialog Corporation

*File 155: format of UD= has changed.

Set Items Description

--- -----

? s adeno or adenovirus

1403 ADENO

11998 ADENOVIRUS

S1 13112 ADENO OR ADENOVIRUS

? s serum(w)free

391996 SERUM

282679 FREE

S2 11938 SERUM(W)FREE

? s s1 and s2

13112 S1

11938 S2

S3 31 S1 AND S2

? t s3/7/16 30 31

3/7/16

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

07837904 93326377

High-level expression of secreted proteins from cells adapted to serum-free suspension culture.

Berg DT; McClure DB; Grinnell BW

Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN

46285-0424.

Biotechniques (UNITED STATES) Jun 1993, 14 (6) p972-8, ISSN 0736-6205

Journal Code: AN3

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We have developed a host cell/vector system based on the use of adenovirus-transformed cells and a promoter, designated GBMT, capable of being activated by the Ela tumor antigen produced in these cells.

GBMT-based vectors were constructed with hygromycin phosphotransferase and murine dihydrofolate reductase as selective markers. We demonstrate their utility in two adenovirus-transformed cell lines, human kidney 293 and Syrian hamster AV12-664. Further, we describe methods and conditions for

the direct adaptation of isolated recombinant clones to serum-free suspension growth conditions. For exemplary purposes, we describe the generation of stable recombinant 293 cell lines with single-copy integrated vectors secreting the highly complex clotting factor human protein C at levels as high as 20 mg/l in serum-free suspension culture. In addition, using the AV12-664 cell line with GBMT and direct dominant selection of the dhfr gene, we have isolated clones secreting a tissue plasminogen activator derivative at levels of about 40 mg/l under serum-free suspension conditions. The distinct advantages of this vector/host cell system are 1) the direct selection of stable clones expressing relatively high levels of recombinant protein, eliminating the need for the tedious stepwise gene amplification process and 2) the direct adaptation to serum-free suspension culture.

3/7/30

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

03758012 81005769

Chemically defined serum-free media for the cultivation of primary cells and their susceptibility to viruses.

Weiss SA; Lester TL; Katter SS; Heberling RL

In Vitro (UNITED STATES) Jul 1980, 16 (7) p616-28, ISSN 0073-5655

Journal Code: GHD

Contract/Grant No.: RR00361, RR, NCCR

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Chemically defined media SFRE-199-1 for the growth and SFRE-199-2 for the maintenance of primary baboon kidney (Bak) cell cultures were formulated by supplementing medium M199 with insulin, sodium pyruvate, zinc sulfate, and increasing arginine-HCl, cysteine, cystine, L-glutamine, L-glutamic acid, glycine, histidine, tyrosine, and glucose to maximally active nontoxic concentrations. For prolonged maintenance of the cells, physiological pH control, and blocking of excessive lactic acid accumulation in the spent medium of the cell cultures, it is necessary to supplement the medium containing Earle's balanced salts with D-(-)-galactose. The cells grew and were maintained equally well on glass or polystyrene surfaces. Selenium, when added to growth medium or substituted for insulin and zinc sulfate, did not stimulate cell growth. Electron microscopy showed that numerous dense particles, approximately 250 to 400 A in diameter, with the appearance of glycogen, were found throughout the cytoplasm in the cells grown in SFRE-199-1 and maintained in SFRE-199-2. Echovirus types 1 to 3, poliovirus types 1 to 3, coxsackievirus types B2, B4, B5, Herpes-virus hominis type 1, simian herpesvirus H, simiae and SA8, and simian adenovirus SV34 when titrated in primary Bak cells and grown and maintained in SFRE-199-1 and 2, respectively, developed titers comparable to those obtained in conventionally grown and maintained cells.

3/7/31

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

02136565 76185015

Autoclavable low cost serum-free cell culture media: the growth of established cell lines and production of viruses.

Keay L

Biotechnol Bioeng (UNITED STATES) Mar 1976, 18 (3) p363-82, ISSN 0006-3592 Journal Code: A6N

Language: ENGLISH

Document type: JOURNAL ARTICLE

Five cell lines (BSC-1, CHO, Balb/c 3T3, HeLa, and KB) have been grown in serum-free media for several months with regular schedules of media changing and subculturing. The medium found to be successful in all cases was MEM-alpha (without the ribosides and deoxyribosides) supplemented with 1% bacteropeptone, although simple MEM (minimum essential medium (Eagle) with bacteropeptone (BP) gave fairly good growth in the case of BSC-1 and 3T3 cells. The addition of insulin was necessary for CHO, 3T3, HeLa, and KB cells. Only the BSC-1 cells grew exclusively as a stationary suspensions and the 3T3 cells growing as a combination of monolayer and suspensions depending on the age of the culture and the nature of the growth surface. SV40 was produced in BSC-1 cells grown and infected in the MEM-alpha, bacteropeptone medium and adenovirus-2 was produced in spinners of HeLa and KB cells grown in MEM-alpha, bacteropeptone, PVP-360, and insulin. The yield of virus and infectivity of the viruses produced were about the same as those produced in conventional serum-containing systems.

? ds

Set Items Description

S1 13112 ADENO OR ADENOVIRUS

S2 11938 SERUM(W)FREE

S3 31 S1 AND S2

? s 293

S4 4082 293

? s s2 and s4

11938 S2

4082 S4

S5 12 S2 AND S4

? t s s7/5

5/7/5

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

08364333 95348517

Rapid expression of an anti-human C5 chimeric Fab utilizing a vector that replicates in COS and 293 cells.

Evans MJ, Hartman SL, Wolff DW, Rollins SA, Squinto SP

Department of Molecular Development, Alexion Pharmaceuticals, Inc., New Haven, CT 06511, USA.

J Immunol Methods (NETHERLANDS) Jul 17 1995, 184 (1) p123-38, ISSN 0022-1759 Journal Code: JFE

0022-1759 Journal Code: JFE

Language: ENGLISH

Document type: JOURNAL ARTICLE

Inhibition of complement system activation requires the development of soluble nonimmunogenic inhibitors with good tissue penetrating abilities that are themselves unable to activate complement. Chimeric mouse/human Fabs capable of blocking the activity of complement proteins are likely to fulfill these criteria. Several monoclonal antibodies that inhibit the activation of the human complement system have recently been developed. To examine the properties of chimeric Fab derived from these monoclonal antibodies, we have developed an expression system which allows the rapid production of milligram quantities of chimeric Fab. Both the chimeric light chain and the chimeric Fd were co-expressed from the same vector, pAPEX-3P. This vector contains the SV40 origin of replication, which allows the rapid production of chimeric Fab in COS cells for preliminary characterization. Additionally, pAPEX-3P contains the Epstein-Barr virus origin of replication and a puromycin selectable marker for maintenance as a stable episome in human cell lines. A production system consisting of transfected 293-EBNA cells cultured in serum free medium followed by protein G-Sepharose chromatography of the conditioned medium was found to be sufficient for the rapid production of purified chimeric Fab. Here we have utilized this expression system to demonstrate that an anti-human C5 chimeric Fab was a potent inhibitor of complement activation in both in vitro activation assays and an ex vivo model of complement-mediated tissue damage.

? ds

Set Items Description

S1 13112 ADENO OR ADENOVIRUS

S2 11938 SERUM(W)FREE

S3 31 S1 AND S2

S4 4082 293

S5 12 S2 AND S4

? s suspen?

S6 43482 SUSPEN?

? s s5 and s6

12 S5

43482 S6

S7 1 S5 AND S6

? t s7/7

7/7/1

DIALOG(R)File 155:MEDLINE(R)

(c) format only 1998 Dialog Corporation. All rts. reserv.

07837904 93326377

High-level expression of secreted proteins from cells adapted to serum-free suspension culture.

Berg DT, McClure DB, Grinnell BW

Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285-0424.

Biotechniques (UNITED STATES) Jun 1993, 14 (6) p972-8, ISSN 0736-6205

Journal Code: AN3

Language: ENGLISH

Document type: JOURNAL ARTICLE

We have developed a host cell/vector system based on the use of adenovirus-transformed cells and a promoter, designated GBMT, capable of being activated by the E1a tumor antigen produced in these cells.

GBMT-based vectors were constructed with hygromycin phosphotransferase and murine dihydrofolate reductase as selective markers. We demonstrate their utility in two adenovirus-transformed cell lines, human kidney 293 and Syrian hamster A V12-664. Further, we describe methods and conditions for the direct adaptation of isolated recombinant clones to serum-free suspension growth conditions. For exemplary purposes, we describe the generation of stable recombinant 293 cell lines with single-copy integrated vectors secreting the highly complex clotting factor human protein C at levels as high as 20 mg/l in serum-free suspension culture. In addition, using the A V12-664 cell line with GBMT and direct dominant selection of the dhfr gene, we have isolated clones secreting a tissue plasminogen activator derivative at levels of about 40 mg/l under serum-free suspension conditions. The distinct advantages of this vector/host cell system are 1) the direct selection of stable clones expressing relatively high levels of recombinant protein, eliminating the need for the tedious stepwise gene amplification process and 2) the direct adaptation to serum-free suspension culture.

? log hold

20jul98 12:29:07 User208669 Session D1217.2

\$6.00 2.000 DialUnits File155

\$0.00 43 Type(s) in Format 6

\$1.00 5 Type(s) in Format 7

\$1.00 48 Types

\$7.00 Estimated cost File155

\$7.00 Estimated cost this search

\$7.16 Estimated total session cost 2.049 DialUnits

Logoff: level 98.07.06 D 12:29:07

? b 357

04aug98 08:43:43 User208669 Session D1234.1

\$0.15 0.045 DialUnits File1

\$0.15 Estimated cost File1

\$0.15 Estimated cost this search

\$0.15 Estimated total session cost 0.045 DialUnits

File 357:Derwent Biotechnology Abs 1982-1998/Aug B2

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Set Items Description

? s ultrafilt?

S1 3253 UL TRAFILT?

? s virus or viruses

22331 VIRUS

3892 VIRUSES

S2 22820 VIRUS OR VIRUSES

? s s1 and s2

3253 S1

22820 S2

S3 170 S1 AND S2

? ds

Set Items Description

S1 3253 UL TRAFILT?

S2 22820 VIRUS OR VIRUSES

S3 170 S1 AND S2

? t s3/7/145

3/7/145

DIALOG(R)File 357:Derwent Biotechnology Abs

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046341 DBA Accession No.: 86-04189

The purification of alpha virus virions and subviral particles using
ultrafiltration and gel exclusion chromatography - potential

application to vaccine preparation

AUTHOR: Crooks A J; Lee J M; Stephenson J R

CORPORATE SOURCE: Vaccine Research and Production Laboratory, Centre for
Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire,
UK.

JOURNAL: Anal Biochem. (152, 2, 295-303) 1986

CODEN: ANBCA2

LANGUAGE: English

ABSTRACT: The introduction of gel exclusion matrices suitable for very
large molecules has enabled chromatographic purification of virus
particles By combining gel exclusion chromatography with

ultrafiltration, a technique for purifying enveloped viruses in a
monodisperse native state has been developed. The process can be used
for production of vaccines of defined immunogenic content. Sindbis
virus (AR 339 isolate) was cultured in suspension cultures of primary
avian fibroblasts. Cultures were centrifuged and the supernatants
treated with sodium azide and aprotinin. They were concentrated and
subjected to Sephacryl S1000 column chromatography, and samples were
examined by PAGE. Purified virus was incubated with Triton X-100 at 4
deg overnight prior to Sephacryl S400 column chromatography. Selected
fractions were concentrated against an XM50 membrane, and fractions
containing the envelope proteins were concentrated and dialyzed prior
to S400 rechromatography. The method gave highly purified, intact alpha
virus particles retaining high levels of biological activity, and was
successfully used for viral envelope protein aggregate preparation. (14

ref)

? t s13/7/16 19 21-24 29 30 37 40 42 49 51 58 62 75 82 84 85 94 102 107 109

S13/7/16 19 21-24 29 30 37 40 42 49 51 58 62 75 82 84 85 94 102 107 109

>>>Set 13 does not exist

? t s3/7/16 19 21-24 29 30 37 40 42 49 51 58 62 75 82 84 85 94 102 107 109

3/7/16

DIALOG(R)File 357:Derwent Biotechnology Abs

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206318 DBA Accession No.: 97-01439

Transduction of nondividing cells using pseudotyped defective high-titer
HIV type 1 particles - HIV virus-1-based vector application in gene

therapy

AUTHOR: Reiser J; Harrison G; Kluepfel-Stahl S; Brady R O; Karlsson S;

Schubert M

CORPORATE AFFILIATE: Nat. Inst Health-Bethesda

Nat. Inst. Neurol. Disord. +Stroke-Bethesda

CORPORATE SOURCE: Building 10, Room 3D04, National Institutes of Health,
Bethesda, MD 20892, USA. email:jreiser@helix.nih.gov.

JOURNAL: Proc.Natl.Acad.Sci.U.S.A. (93, 26, 15266-71) 1996

ISSN: 0027-8424 CODEN: PNASA6

LANGUAGE: English

ABSTRACT: replication-defective HIV virus-1-based vectors were used to
deliver genes into nondividing cells. The vectors were designed to
carry a neomycin-phosphotransferase reporter gene or thermostable
antigen in place of the g160 gene of HIV virus-1. The vectors also
contained inactive vpr, vpu and nef encoding regions. Pseudotyped HIV
virus-1 particles carrying either the ecotropic or the amphotropic
mouse Moloney leukemia virus (MLV) envelope proteins or the
vesicular-stomatitis virus G protein were released after single or
double transfections of either human 293T or monkey COS-7 cells with
titers of up to 10 million cfu/ml. A simple ultrafiltration procedure

gave an additional 10- to 20-fold concentration of the pseudotyped particles. These vectors and the MLV-based vectors were used to transduce primary human skin fibroblasts and human peripheral blood CD34+ cells. The HIV virus-1 vector system was more effective than its MLV-based counterpart in transfecting G0 and G1 stage cells. (56 rel)

3/7/19

DIALOG(R)File 357:Derwent Biotechnology Abs

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201582 DBA Accession No.: 96-12353

Production of increased titer retro virus vectors from stable producer cell lines by superinfection and concentration - retro virus vector transfection into amphotropic or ecotropic envelope glycoprotein-gene expressing packaging cell culture for rat beta-glucuronidase gene transfer; application in gene therapy

AUTHOR: Parente M K; +Wolfe J H

CORPORATE AFFILIATE: Univ: Pennsylvania

CORPORATE SOURCE: Department of Pathobiology and the Center for Comparative Medical Genetics, School of Veterinary Medicine, University of Pennsylvania, 3800 Spruce Street, Philadelphia, PA 19104, USA.

JOURNAL: Gene Ther. (3, 9, 756-60) 1996

ISSN: 0969-7128 CODEN: 4352W

LANGUAGE: English

ABSTRACT: Retro virus vector (e.g. plasmid NTK-BGEO) titers were increased over 50-fold by packaging cell culture superinfection and concentration. The vector expressed a neo gene from a long terminal repeat promoter and a rat beta-glucuronidase (EC-3.2.1.31) gene from an internal TK promoter. NTK-BGEO was transfected into helper virus-free packaging cells expressing an amphotropic (GP+envAM12 cells) or ecotropic (GP+E86 cells) envelope glycoprotein gene. High level expression was stable for at least 90 passages in culture. The optimum conditions for cell seeding density, length of incubation and temporary storage of virus-containing medium were determined. The vector preparation was concentrated a further 20-fold in ultrafilters with mol.wt. cutoffs of 30-1,000 kDa. The ultrafilters were tested for concentrating ability and for concentrate toxicity on target cells. These methods may be used to produce vectors containing retro virus envelope proteins in ml volumes at titers in excess of 100 million cfu/ml and in l volumes greater than 1 million cfu/ml. (14 rel)

3/7/21

DIALOG(R)File 357:Derwent Biotechnology Abs

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197980 DBA Accession No.: 96-08751

Proteoglycans secreted by packaging cell lines inhibit retro viral-mediated gene transfer - retro virus purification by ultrafiltration for proteoglycan removal for subsequent gene transfer to NIH3T3 cell

culture; potential gene therapy (conference abstract)

AUTHOR: Le Doux J M; Morgan J R; Yarnush M L

CORPORATE AFFILIATE: Univ:New-Jersey-State Gen.Hosp Boston

Shriners-Burns-Inst Boston

CORPORATE SOURCE: Department of Chemical and Biochemical Engineering, Rutgers University, Piscataway, NJ 08854, USA.

JOURNAL: Abstr Pap Am Chem Soc. (211 Meet, Pt.1, BIOT224) 1996

ISSN: 0065-7727 CODEN: ACSRAL

CONFERENCE PROCEEDINGS: 211th ACS National Meeting, New Orleans, LA, 24-28

March, 1996.

LANGUAGE: English

ABSTRACT: Methods to increase the efficiency of retro virus-mediated gene transfer to NIH3T3 cells using a recombinant mouse retro virus that encodes the beta-galactosidase LacZ gene was studied. A soluble inhibitor, secreted into the culture medium by NIH3T3 and packaging cell lines, limited retro virus infection. The inhibitor was present in retro virus stocks and reduced their transduction efficiency at least 2-fold. The inhibitor was large (over 100 kDa) and sensitive to chondroitin-ABC-lyase, suggesting that it was a proteoglycan secreted by the packaging cell lines. Concentration of retro virus stocks by ultrafiltration co-concentrates virus particles and proteoglycans and selective removal of proteoglycans from these concentrated retro virus stocks improves their transduction efficiency significantly. The highly efficient retro virus stocks may facilitate gene therapy protocols, which require insertion of multiple gene copies per target cell for maximum biological effectiveness. (0 rel)

3/7/22

DIALOG(R)File 357:Derwent Biotechnology Abs

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196777 DBA Accession No.: 96-08157

Optimization of environmental factors for the production and handling of recombinant retro virus - for application in human gene therapy

AUTHOR: Lee S G; Kim S; +Kim B G; Robbins P D

CORPORATE AFFILIATE: Univ:Seoul-Nat Inst Mol Biol Genet Univ:Pittsburgh

CORPORATE SOURCE: Institute for Molecular Biology and Genetics, Seoul

National University, Seoul 151-742, Korea.

JOURNAL: Appl Microbiol Biotechnol. (45, 4, 477-83) 1996

ISSN: 0175-7598 CODEN: EJABDD

LANGUAGE: English

ABSTRACT: Steps involved in psiCIP/MPG-lacZ retro viral gene delivery, from retro virus vector (RVV) production to infection, were investigated to identify factors affecting RVV titer during virus production and its handling. RVV titers were highest when the culture supernatant was harvested 3 days after the producer cells had reached confluence. About a 2-fold increase in vector production was achieved

at 32 deg compared to that at 37 deg. Low serum concentrations had no significant effect on the titers of virus produced by the CRIP cell line. RRVs were stable at 4 deg but very unstable at 37 deg and were quite sensitive to freezing and thawing. Increase in viral exposure time for infection to target NIH3T3 cells was linearly proportional to the RVV titer for up to 15 hr. Using DEAE-dextran in place of polybrene as a polycation during infection enhanced infection efficiency about 3-fold. The retro virus was robust to simple ultrafiltration and its titer was easily concentrated 16-fold. Despite a loss of 50% during the freezing/thawing step, a RVV titer of 10(8) to 10(9) was easily obtained. At least a 100-fold increase in titer could be achieved with simple optimization. (13 ref)

3/7/23

DIALOG(R)File 357:Derwent Biotechnology Abs

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196159 DBA Accession No.: 96-06930

A rapid and efficient method for concentration of small volumes of retroviral supernatant - retro virus vector supernatant concentration using ultrafiltration membrane; application in gene therapy

AUTHOR: Miffler D L, Melkle P J, +Anson D S

CORPORATE AFFILIATE: Women's+Child Hosp North-Adelaide
CORPORATE SOURCE: Department of Chemical Pathology; Adelaide Women's and Children's Hospital, 72 King William Road, North Adelaide, SA 5006, Australia

JOURNAL: Nucleic Acids Res. (24, 8, 1576-77) 1996

ISSN: 0305-1048 CODEN: NARHAD

LANGUAGE: English

ABSTRACT: A rapid and efficient method was developed for the concentration of small volumes of retro virus supernatant. This method used ultrafiltration membranes with a 100,000 mol.wt. cut off (YM100). The filter was prewashed with 100 ml deionized water and 50 ml phosphate buffered saline. Retro viruses were harvested in DMEM media without phenol red, pooled and prefiltered through a 0.45 um filter to remove any cells and debris. The filtrate was then added to a stirred cell system with a YM100 membrane and concentrated under nitrogen pressure (500 kpa) with gentle stirring until the desired volume was reached. The concentration system was held at 4 deg to minimize loss of retro virus viability. The final volume was 2 ml from a starting volume of 100-150 ml and the concentration time was 2.5 hr. The resulting supernatant did not cause any loss of target cell viability. Many current gene therapy protocols use retro viruses as vectors to package and transfer genes to target cells. (1 ref)

3/7/24

DIALOG(R)File 357:Derwent Biotechnology Abs

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194906 DBA Accession No.: 96-05677 PATENT

Pure influenza antigen preparation by ultrafiltration of viral suspension - influenza virus antigen purification; useful in vaccine and as diagnostic reagents

AUTHOR: Violay J M, Court G, Gerdil C, Chalumeau H, McVerry P
CORPORATE SOURCE: Lyon, France

PATENT ASSIGNEE: Pasteur-Merieux-Serums-Vaccines 1996

PATENT NUMBER: WO 9605294 PATENT DATE: 960222 WPI ACCESSION NO.: 96-139692 (9614)

PRIORITY APPLIC. NO.: FR 9410039 APPLIC. DATE: 940816

NATIONAL APPLIC. NO.: WO 95US727 APPLIC. DATE: 950606

LANGUAGE: French

ABSTRACT: Preparation of purified influenza virus (IV) antigens (A) from a liquid containing IV comprises (a) purification by ultracentrifugation, filtration step, and/or (b) fragmentation of live virus in the presence of an amphiphilic, nonionic surfactant (f) then elimination of undesirable components before filtration that retains all the viral components. If both steps (a) and (b) are used, they may be done in either order. (f) is preferably octoxynol-9 (Triton X-100). In a preferred process, comprising step (a) only or steps (a) and (b), the virus composition is particularly purified by zonal centrifugation, especially in a sucrose gradient at about 9,000 x g, then filtered (down to a minimum pore size of 0.3 um) and ultracentrifugation repeated. The resulting viral suspension is standardized (to a protein concentration of 0.2-1 ng/ml) using buffer (phosphate-buffered saline) and fragmented at 20-25 deg by the addition of (f). Undesirable components are removed by diafiltration. The starting material is particularly allantoic fluid from embryonated eggs being used to cultivate the virus. (A) are used to make IV vaccines or diagnostic reagents. (17pp)

3/7/29

DIALOG(R)File 357:Derwent Biotechnology Abs

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178911 DBA Accession No.: 95-06321

Ultrafiltration as a useful step for the purification of recombinant proteins during downstream processing of cell culture supernatants - purification of two Epstein-Barr virus surface proteins from recombinant Chinese hamster ovary cells using a protein-free medium (conference abstract)

AUTHOR: Scharfenberg K, Wagner R

CORPORATE AFFILIATE: Ges.Biotechnol.Forsch.

CORPORATE SOURCE: Cell Culture Techniques Dept., Gesellschaft fuer Biotechnologische Forschung m.b.H., Mascheroder Weg 1, D-38124 Braunschweig, Germany.

JOURNAL: Cytotechnology (14, Suppl.1, 5, 18) 1994

ISSN: 0920-9069 CODEN: 3514D

CONFERENCE PROCEEDINGS: Animal Cell Technology: Developments Towards the 21st Century, Veldhoven, The Netherlands, 14-16 September, 1994.

LANGUAGE: English

ABSTRACT: High mol wt. proteins secreted from mammalian cells growing in protein-free culture medium formulations were efficiently purified by ultrafiltration as a first step in a downstream process. Simultaneous purification of 2 highly glycosylated Epstein-Barr virus surface proteins of 250 and 350 kDa, respectively, from recombinant CHO cells was carried out. The products were efficiently concentrated using a membrane with a nominal mol.wt. cut-off value of 100,000 by removing nearly all low mol.wt. proteins (purification factor greater than 2) such that only 2 additional chromatographic procedures were necessary for achieving homogeneity of the 2 glycoproteins. (0 ref)

3/7/30

DIALOG(R)File 357:Derwent Biotechnology Abs

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178332 DBA Accession No.: 95-05153 PATENT

Respiratory-synechial virus immunogenic composition - growth in Vero cell culture, and purification by microfiltration, tangential flow

ultrafiltration, centrifugation and chromatography for use as a vaccine

AUTHOR: Sahuzeza S E; Ewasystyn M E; Klein M H

PATENT ASSIGNEE: Connaught 1995

PATENT NUMBER: WO 9504545 PATENT DATE: 950216 WPI ACCESSION NO.:

95-090684 (9512)

PRIORITY APPLIC. NO.: US 102742 APPLIC. DATE: 930806

NATIONAL APPLIC. NO.: WO 94CA425 APPLIC. DATE: 940804

LANGUAGE: English

ABSTRACT: A non-immunopotentiating immunogenic composition capable of producing a respiratory-synechial virus (RSV)-specific immune response may be produced by: growing RSV in a cell line, harvesting the virus; purifying the virus under non-denaturing conditions, free of cellular and serum components; inactivating the virus with an inactivating agent (e.g. beta-propiolactone, a nonionic surfactant, e.g. n-octyl-alpha-D-glucopyranoside or n-octyl-beta-D-glucopyranoside, or ascorbic acid), to give non-infectious, non-immunopotentiating and immunogenic RSV; and formulating the RSV into a composition. The cell line is a continuous cell culture of vaccine quality, e.g. Vero cell culture. Purification involves microfiltration to remove cell debris, tangential flow ultrafiltration (100,000-300,000 mol.wt. cutoff membrane) to remove serum components, pelleting by ultracentrifugation to remove further serum components, and subjecting the pelleted material to sucrose density gradient centrifugation. Gel filtration and ionexchange chromatography steps may be included. The product may be used as a vaccine or diagnostic agent. (38pp)

3/7/37

DIALOG(R)File 357:Derwent Biotechnology Abs

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163991 DBA Accession No.: 94-06542

Bioseparation steps in processing proteins and other biological products.

Part 2: initial fractionation - protein purification; a review

AUTHOR: Sadana A

CORPORATE AFFILIATE: Univ. Mississippi

CORPORATE SOURCE: Chemical Engineering Department, University of Mississippi, 135 Anderson Hall, University, MS 38677-9740, USA.

JOURNAL: Biopharm Manuf. (7, 3, 34-43) 1994

CODEN: BPRME5

LANGUAGE: English

ABSTRACT: A review of procedures used to separate proteins and biologics is presented. Attention is focused on efforts to reduce development times and processing costs. The following are discussed: i. isolation steps (an overview) - aq.; two-phase partitioning; ii. membrane separation - protein recovery using microporous membranes; virus removal from protein solutions using membranes; clarification of fermentation broth for antibody production using ultrafiltration, two-phase systems, extraction of benzylpenicillin by an emulsion liquid membrane process, a traditional purification process for insulin production, affinity precipitation using chitosan as a ligand adsorbent for protein purification, affinity precipitation method for proteins by surfactant-solubilized, ligand-modified phospholipids, using modified divinylbenzene-polystyrene resins for the separation of aspartame, phenylalanine, aspartic acid and asparagine, ultrafast HPLC separation for recombinant DNA-derived proteins. (48 ref)

3/7/40

DIALOG(R)File 357:Derwent Biotechnology Abs

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152064 DBA Accession No.: 93-10116

Depth filters in downstream processing: an efficient through-flow filtration method - depth filter characterization and suitability e.g. for mammal cell culture processing

AUTHOR: Martin J

CORPORATE AFFILIATE: Pall-Ultraline-Filtration

CORPORATE SOURCE: Pall Ultraline Filtration Company, East Hills, NY, USA.

JOURNAL: BioTechnology (11, 7, 843-45) 1993

CODEN: BTCHDA

LANGUAGE: English

ABSTRACT: The Pall Profile II absolute-rate, graded pore depth filter cartridge is characterized with its respect to its use for the removal of mammalian cells and cell debris at high flow rates under low shear conditions. The advantages of this depth filter include: operation at ambient temp.; high separation efficiency; rapid processing; negligible shear effect; efficiency independent of cell size or density; the lack

of a requirement for processing aids; sterile containment; in situ steam sterilization; compact, simple, reliable equipment; disposable elements; low investment cost; high product recovery with low hold-up; direct scalability; and absolute removal ratings. The filter protects downstream membrane filters that are used to remove residual submicron debris, bacteria and viruses, and sterilize product intermediates and buffers. They can also protect ultrafilters and chromatography columns from contamination and premature fouling and reduce the risk of endotoxin contamination from buffers and other fluids. The filter can be used from pilot scale to production processes. (0 ref)

3/7/42

DIALOG(R)File 357:Derwent Biotechnology Abs

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151161 DBA Accession No.: 93-09213 PATENT

Preparation of foot-and-mouth-disease virus vaccine - growth in BHK21-C13 cell culture

PATENT ASSIGNEE: Inst.Cercet Vaccinuri-Bioprep, Pasteur 1992

PATENT NUMBER: RO 104376 PATENT DATE: 920125 WPI ACCESSION NO.: 93-173561

(9321)

PRIORITY APPLIC. NO.: RO 136768 APPLIC. DATE: 881222

NATIONAL APPLIC. NO.: RO 136768 APPLIC. DATE: 881222

LANGUAGE: Romanian

ABSTRACT: A vaccine for immunization of ruminants against foot-and-mouth-disease virus (FMDV) contains an inactivated virus, obtained from FMDV A5/D/C subtype grown in a BHK21-C13 S-G-84 cell culture. The viruses are grown a BHK cell monolayer for 16-24 hr, preferably 18-20 hr, or in suspension cell culture for 9-24 hr, concentrated by ultrafiltration on aluminum hydroxide or bentonite at pH 7.6-8.5, agitated for 2-12 (preferably 4-6) hr and allowed to stand overnight. The pH is corrected to 8.2-8.5, and viruses are inactivated with a 0.01 M solution of binary ethyleneimine. After 24 hr, this is neutralized by 4 ml/l sterile 50% sodium thiosulfate solution. The product is optionally used as a monovalent vaccine at a dose of 1-2 ml, or used to produce a trivalent vaccine, with a dose of 5-6 ml, with aluminum hydroxide forming 30-50% of the volume, ensuring the presence of 1.6 wt.% Al₂O₃ and 0.06 g saponin/ml.

3/7/49

DIALOG(R)File 357:Derwent Biotechnology Abs

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146360 DBA Accession No.: 93-04412

Baculo virus-expressing herpes simplex virus type 2 glycoprotein D is immunogenic and protective against lethal HSV challenge - recombinant vaccine preparation using Spodoptera frugiperda cell culture

AUTHOR: Landolf V, Zarley C D, Abramovitz A S, Figueroa N, Wu S L, +Mishkin E M

CORPORATE AFFILIATE: Lederle-Praxis-Biol.

CORPORATE SOURCE: Department of Viral Vaccine Research and Development, Lederle-Praxis-Biologics, Pearl River, NY 10965, USA.

JOURNAL: Vaccine (11, 4, 407-14) 1993

CODEN: VACCDE

LANGUAGE: English

ABSTRACT: The glycoprotein D (gD) of herpes simplex virus type 2 was expressed in Spodoptera frugiperda Sf9 cells by the recombinant baculo virus D2Ac-11, generated by replacing the polyhedrin gene of Autographa californica nuclear-polyhedrosis virus (AcNPV) with the gD2 gene under the control and regulation of the polyhedrin promoter. Sf9 cells were co-transfected with wild-type AcNPV and the recombinant baculo virus (plasmid p941gD2C), and occlusion body-negative plaques were amplified on Sf9 cells. Resultant plaques were screened for baculo virus gD2 expression by SDS-PAGE and by Western or dot blotting of cell lysates using a gD-specific monoclonal antibody. Recombinant baculo virus D2Ac-11 was selected for further examination. Recombinant gD was recovered from infected Sf9 cells by surfactant solubilization, tangential flow ultrafiltration, ionexchange chromatography, and immunoaffinity chromatography. The resultant purified gD existed as a homogeneous mol.wt. 57,500 monomer. The baculo virus-expressed gD2 was demonstrated to be an immunogenic and protective vaccine candidate in a BALB/c mouse model of HSV2 infection. (43 ref)

3/7/51

DIALOG(R)File 357:Derwent Biotechnology Abs

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145982 DBA Accession No.: 93-04034

SF-1, a low cost culture medium for the production of recombinant proteins in baculo virus infected insect cells - use for Spodoptera frugiperda Sf9 and Sf21 cell culture

AUTHOR: Schlaeger E J, Foggetta M, Vonach J M, Christensen K

CORPORATE AFFILIATE: Roche

CORPORATE SOURCE: F. Hoffmann-La Roche Ltd., PRTM 66/108, CH - 4002 Basel, Switzerland.

JOURNAL: Biotechnol. Tech. (7, 3, 183-88) 1993

CODEN: BTECE6

LANGUAGE: English

ABSTRACT: IP301 and SF-1 culture media were compared for the cultivation of Spodoptera frugiperda Sf9 and Sf21 cells. The semi-defined IP301 medium, and SF-1, a medium based on ultrafiltered protein lysates and containing 1/10 IP301, were supplemented with lipids and Pluronic F68. The low cost SF-1 medium was easy to prepare and showed very little lot to lot variation. After 3-5 passages, Sf9 and Sf21 cells were fully adapted and grew in the presence of 1-1.5 serum, or in protein-free

media, to high cell numbers. Doubling times were 22-25 hr, and final cell densities were 10-13 million cells/ml. Production of recombinant proteins was examined using SF9 and Sf21 cells infected with a recombinant Autographa californica nuclear-polyhedrosis virus vector carrying a gene encoding human soluble tumor necrosis factor receptor-alpha. Yields of the recombinant protein in serum-free SF-1 were similar to, or slightly higher than, those obtained using other commercial media. In airlift culture vessels (23 l) using serum-free SF-1, Sf9 cell density reached 10 million viable cells/ml; this increased to 13 million cells/ml in SF-1 + 1.5% serum. (7 ref)

3/7/58

DIALOG(R)File 357:Derwent Biotechnology Abs

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135837 DBA Accession No.: 92-08329 PATENT

Tangential flow filtration process and apparatus - operates at a flux of 5-100% of transition point flux to separate a species of interest (e.g. microorganism, mammal cell, DNA, RNA) from a mixture

PATENT ASSIGNEE: Genentech 1992

PATENT NUMBER: WO 9204970 PATENT DATE: 920402 WP1 ACCESSION NO.: 92-131929 (9216)

PRIORITY APPLIC. NO.: US 583886 APPLIC. DATE: 900917

NATIONAL APPLIC. NO.: WO 91US6553 APPLIC. DATE: 910911

LANGUAGE: English

ABSTRACT: A tangential flow filtration (TFF) process uses a membrane having a pore size that separates the species of interest (mol. wt. 1,000-1,000,000 or 0.1-10 um) from a mixture while maintaining flux at a level of 5-100% of the transition point (TP) flux. Preferably, the transmembrane pressure (TMP) is constant along the membrane at a level no greater than the TMP at the TP of the filtration, 2 membranes of the same pore size are layered in parallel, and the flux is 75-100% of the TP flux. Microorganisms, mammalian cells, proteins, peptides, amino acids, colloids, mycoplasma, endotoxins, viruses, carbohydrates, RNA and DNA may be purified from an undiluted mixture, and may be less than 10 times larger or smaller in mol. wt. than the other species of the mixture. The retentate can be recycled. A 2nd and 3rd TFF may be performed using membranes of sequentially smaller pore size. All 3 steps are preferably ultrafiltrations. An apparatus for the process is also claimed. Maintenance of TMP within the pressure-dependent region of the flux versus TMP curve decreases retention of molecules of mol. wt. lower than the membrane rating and improves selectivity. (48pp)

3/7/62

DIALOG(R)File 357:Derwent Biotechnology Abs

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133093 DBA Accession No.: 92-05585

Strategies for improved production of Epstein-Barr virus - in B95-8 cell

culture and purification by tangential flow filtration and ultrafiltration using polysulfone membrane; potential application in vaccine production (conference paper)

AUTHOR: Davies A H; Huddleston J; Evans F J; Rickinson A B; Emery A N
CORPORATE SOURCE: Institute of Virology, Mansfield Road, Oxford OX1 3SR, UK.

JOURNAL: Prod Biol Anim Cells Cult. (ESACT 10 Meet., 706-08) 1992

CODEN: 9999Z

LANGUAGE: English

ABSTRACT: Large-scale production of Epstein-Barr virus (EBV) for study has been hampered by the lack of a simple permissive tissue culture system. Conventional strategies for enhancing the EBV population of B95-8 cells (EBV-infected marmoset B-lymphocytes), by addition of tumor promoter TPA and ultracentrifugation, are labor intensive and give low yields. A highland analog of TPA, designated SapA, was identified as an equipotent active analog for EBV induction in B95-8 cells which lacked the tumor promoting function of TPA. Contained separation of B95-8 cells from culture fluid was achieved by tangential flow filtration using microporous membranes (pore size 0.45 um) and the Minimat flat membrane system. EBV particles (average size 100 nm) in the resulting permeate were concentrated using polysulfone ultrafiltration membranes in the same equipment. Attempts to concentrate virus over a 100 kDa MWCO (mol. wt. cut-off) membrane failed, but the use of a 300 kDa MWCO membrane was successful. This procedure may be useful in the production of the EBV lytic antigen, gp350, which has long been considered a potential anti-EBV vaccine. (0 ref)

3/7/75

DIALOG(R)File 357:Derwent Biotechnology Abs

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122545 DBA Accession No.: 91-10187 PATENT

Composite membrane for selectively removing particles from solution - virus isolation using e.g. a hollow fiber membrane composite having a porous membrane substrate, a surface skin for ultrafiltration and an intermediate porous zone

PATENT ASSIGNEE: Millipore 1991

PATENT NUMBER: US 5017292 PATENT DATE: 910521 WP1 ACCESSION NO.: 91-171130 (9123)

PRIORITY APPLIC. NO.: US 521784 APPLIC. DATE: 900510

NATIONAL APPLIC. NO.: US 521784 APPLIC. DATE: 900510

LANGUAGE: English

ABSTRACT: A composite, asymmetric membrane selectively separates virus particles from a solution produced e.g. by mammal cell culture. The membrane has a substrate of average pore size 0.05-10 um, a surface skin having ultrafiltration properties and an intermediate zone which has an average pore size smaller than that of the substrate, and which is free of voids which break the skin and which directly communicate

with the substrate. The membrane has a protein mol.wt. cut-off of 500-5,000,000. It is capable of 99.9% removal of particles of 10-100 nm diameter. Selectivity and reproducibility are higher than those obtained by conventional membranes. The membrane is produced by a casting a 10-21% polymer solution onto a microporous membrane. The substrate is preferably polyvinylidene difluoride (the intermediate zone and skin may be formed of the same material). A flat sheet or a hollow fiber membrane construct is formed. When protein solution contacts the membrane skin, particles are retained. The particle-rich solution is either recycled or directed to a second, similar composite membrane. Particle-free solute passes through the skin. (22pp)

3/7/82

DIALOG(R)File 357:Derwent Biotechnology Abs

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116153 DBA Accession No.: 91-03795

Developments in foot-and-mouth-disease vaccines - foot-and-mouth-disease virus culture in Frenkel, BHK, IBRS2, Hml.u, NIL-2 monolayer or suspension cell culture; attenuated live or recombinant vaccine construction, review

AUTHOR: Barteling S.J.; Vreeswijk J

CORPORATE SOURCE: Central Veterinary Institute, Virology Complex, P.O. Box 365, 8200 AJ, Lelystad, The Netherlands.

JOURNAL: Vaccine (9, 2, 75-88) 1991

CODEN: VACCDE

LANGUAGE: English

ABSTRACT: The current status of foot-and-mouth-disease virus (FMDV) vaccine production is reviewed. Antigen production in cattle tongue epithelium (Frenkel culture), and improvements in baby hamster kidney (BHK), pig kidney IBRS2, hamster lung Hml.u, hamster embryo NIL-2 monolayer and suspension cell culture are discussed. Inactivation of virus antigens e.g. by aziridines or formaldehyde, and safety tests are discussed. A minimum safety level is recommended: at the end of the inactivation process, antigen batches should contain less than 1 virus particle. After inactivation, the antigen can be formulated into a vaccine or purified and concentrated (chloroform treatment, sedimentation of Al(OH)₃-antigen complex, ultrafiltration and precipitation using PEG or polyethylene oxide) for storage at ultra-low temp. in a vaccine bank. Vaccines prepared with the adjuvants Al(OH)₃ and saponin are compared with the oil emulsion vaccines. Because oil vaccines can protect both cattle and pigs for a long term, they are used for ring vaccination. New recombinant vaccines are based on modified-live viruses or biosynthetic peptides. (191 ref)

3/7/84

DIALOG(R)File 357:Derwent Biotechnology Abs

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113134 DBA Accession No.: 91-00776 PATENT

Removal of cellular DNA from virus suspension - hepatitis A virus and Russian tick-borne encephalitis virus culture, vaccine preparation, isolation and purification, DNA removal by gel filtration chromatography and centrifugation

PATENT ASSIGNEE: Inst.Polio-Viral-Encephalitis 1989

PATENT NUMBER: SU 1532050 PATENT DATE: 891230 WPI ACCESSION NO.: 90-326472 (9043)

PRIORITY APPLIC. NO.: SU 4396256 APPLIC. DATE: 880324

NATIONAL APPLIC. NO.: SU 4396256 APPLIC. DATE: 880324

LANGUAGE: Russian

ABSTRACT: Russian tick-borne encephalitis virus or hepatitis A virus is grown at 37 deg for 48-72 hr or 14 days, respectively, in a suspension cell culture which is permissive for the virus and authorized for vaccine production. The virus is then concentrated and ballast impurities are removed by centrifugation at 5,000-1,000 g, or by membrane filtration (pore diameter 200-500 nm) and ultrafiltration (pore diameter 5-50 nm). Protamine sulfate up to 4 mg/ml is added to the concentrate and the mixture is incubated at 4 deg for 30 min. The formed deposit is removed by centrifugation at 4,000-12,000 g for 30 min. Residues of cellular DNA are removed by centrifuging at 75,000 g for 3 hr on a 15% sucrose gradient or by gel chromatography on Sepharose-6B. The concentration of cellular DNA at each stage is measured by 'precise hybridization' (sensitivity 2.5 pg/ml). The cellular DNA content of encephalitis virus isolates is reduced from 1-3 ug/ml to 200-400 pg/ml and that of hepatitis A virus is reduced to 1-9 pg/ml. The simple method is useful in vaccine production for removal of cellular DNA. (5pp)

3/7/85

DIALOG(R)File 357:Derwent Biotechnology Abs

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113133 DBA Accession No.: 91-00775 PATENT

Production of Japanese-encephalitis vaccine - Japanese-encephalitis virus vaccine

PATENT ASSIGNEE: Takeda-Chem. 1990

PATENT NUMBER: JP 2223531 PATENT DATE: 900905 WPI ACCESSION NO.: 90-315980 (9042)

PRIORITY APPLIC. NO.: JP 89291443 APPLIC. DATE: 891109

NATIONAL APPLIC. NO.: JP 89291443 APPLIC. DATE: 891109

LANGUAGE: Japanese

ABSTRACT: The production of Japanese-encephalitis virus (JEV) is claimed where a suspension of JEV from mouse brain emulsion is subjected to a hydrophobic ultrafiltration membrane (UM) with a stabilizer and then filtered again using a UM treated with strong alkali (NaOH, KOH). More specifically, the vaccine has a titer of 1000 or more in 20 ug/ml of protein. JEV suspension is prepared from protamine sulfate (e.g. 1.2

mg/ml) and homogenized JEV-infected mouse brain emulsion. The stabilizer is 0.1-2.5 wt./vol.%, especially 0.2-1.0 wt./vol. of e.g. erythritol, mannitol, sorbitol or inositol, or 0.004-0.1 wt./vol.%, especially 0.01-0.05 wt./vol. of gelatin. Vaccine with improved titer and thermostability is produced. In an example, JEV suspension mixed with gelatin and sorbitol was filtered through hydrophobic polysulfone ultrafiltration resin TS-300. Resulting formalin-deactivated JEV was filtered on brain protamine-pretreated UM and then on NaOH-pretreated UM. Diluent was added and the process repeated 5-6-fold to obtain a solution which was mixed with 0.01 wt./vol.% thimerosal and 0.05 wt./vol.% Tween 80 to form a vaccine base solution. (5pp)

3/7/94

DIALOG(R)File 357:Derwent Biotechnology Abs

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107259 DBA Accession No.: 90-09950 PATENT

Virus antigen recovery from cell culture - Marek-disease virus purification from fowl fibroblast cell culture by calcium phosphate and polyethylene glycol precipitation; potential disease diagnosis and vaccine construction

PATENT ASSIGNEE: VEB-Friedrich-Loeffler-Inst. 1989

PATENT NUMBER: DD 274356 PATENT DATE: 891220 WPI ACCESSION NO.: 90-164408

(9022)

PRIORITY APPLIC. NO.: DD 318354 APPLIC. DATE: 880727

NATIONAL APPLIC. NO.: DD 318354 APPLIC. DATE: 880727

LANGUAGE: German

ABSTRACT: The production of virus antigens from capsular viruses is effected by culturing virus-infected cells, disrupting the cells, treating the cell-free supernatant with 0.1-5% calcium phosphate, removing the precipitate, treating the supernatant with 2-16% PEG 2,000-300,000, and removing the sediment. The supernatant may be concentrated by ultrafiltration. The antigen preparations may be used in disease diagnosis or in vaccine construction. Despite being only partially purified, the antigens give sharply defined immunodiffusion bands. In an example, a young fowl fibroblast cell culture was infected with Marek-disease virus in 100 ml of a medium containing 15% cattle serum. The suspension was subjected to a freeze-thaw cycle, sonicated and centrifuged at 3,000 rpm for 10 min. The supernatant was treated with 20 ml of 1% calcium phosphate, stirred at 4 deg for 20 min, and centrifuged at 4,000 rpm for 20 min. The supernatant was treated with 8% PEG 6,000, kept at 4 deg for 16 hr, and centrifuged. (3pp)

3/7/102

DIALOG(R)File 357:Derwent Biotechnology Abs

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100470 DBA Accession No.: 90-03161

Semipurified human leukocyte ultrafiltrate in herpes zoster. I. Large-scale preparation and biochemical analysis - herpes zoster virus vaccine preparation

AUTHOR: Borvak J, Mayer V, Kotlik J

CORPORATE SOURCE: Institute of Virology, Slovak Academy of Sciences, 817 03 Bratislava, Czechoslovakia.

JOURNAL: Acta Virol. (33, 5, 417-27) 1989

CODEN: AVIRA2

LANGUAGE: English

ABSTRACT: 9 Batches of lysed human leukocyte ultrafiltrate (LLU) prepared from disrupted buffy coats of random healthy donors by ultrafiltration, as well as their semi-purified subfractions (P2/II), were compared in terms of protein, orcinol-reactive material (ORM) content and ratios of their ORM and protein contents. The fractions were purified by ethanol precipitation and gel filtration chromatography on Sephadex G-15. A 4.4-fold increase in the ORM/protein ratio of P2/II was obtained. High variation in protein and ORM content of crude batches was observed. The purification procedure removed 85% proteins and 33% ORM from the LLU. The material removed contained inhibitors of the cell-mediated immunity-inducing and/or augmenting properties of LLU. This was in good agreement with the observed improved therapeutic effect of P2/II fraction in herpes zoster treatment in otherwise non-compromised adults. (37 ref)

3/7/107

DIALOG(R)File 357:Derwent Biotechnology Abs

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096117 DBA Accession No.: 89-14108

Equipment design of biological liquids separation by means of ultrafiltration on hole fibers - diafiltration, concentration, purification

AUTHOR: Petrov S V, Zenkevich V B, Sakulina L M

CORPORATE SOURCE: Pilot-scale Design Bureaux of Fine Biological Engineering, Kirishi, Leningrad Region, USSR.

JOURNAL: Biokhimiya (5, 4, 485-91) 1989

CODEN: BTKNEZ

LANGUAGE: Russian

ABSTRACT: The design of equipment for the separation of biological fluids by ultrafiltration on hole fibers is discussed. Fiber VPU-15PA based on an aromatic polyamide (phenion S-2) was used. Schematic representations of devices for batch and continuous concentration of solutions and for diafiltration are presented. Features and limitations of devices based on hole fibers are considered. Reference is made to the use of hole fibers for concentration of influenza virus suspensions in allantoic fluid during the production of inactivated influenza vaccine, purification of hydroxyethyl starch by diafiltration, protein concentration, and removal of cell fragments from baker's yeast

(Saccharomyces cerevisiae) autolyzate. The equipment described may be used for concentration, purification, and isolation of a wide range of biological materials. (8 ref)

3/7/109

DIALOG(R)File 357:Derwent Biotechnology Abs

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095170 DBA Accession No.: 89-13161 PATENT

A method for virus purification utilizing hydrophobic ultrafiltration membrane - application in vaccine production

PATENT ASSIGNEE: Toyo-Soda 1989

PATENT NUMBER: JP 1174379 PATENT DATE: 890710 WPI ACCESSION NO.: 89-238832 (8933)

PRIORITY APPLIC. NO.: JP 87334904 APPLIC. DATE: 871228

NATIONAL APPLIC. NO.: JP 87334904 APPLIC. DATE: 871228

LANGUAGE: Japanese

ABSTRACT: A new method for purifying viruses comprises filtering a virus suspension containing soluble protein with an asymmetric membrane, composed of polyvinyl formal resin of mol wt. 2-5 million. Using the new method, proteins derived from cells or tissues and cattle serum albumin are removed. The highly purified viruses can be used as vaccines. In an example, rabies virus vaccine strains derived from baby hamster kidney (BHK-21) cell culture were sensitized by viruses and cultured in Eagle's medium containing 10% fetal cattle serum at 37 deg for 5 days. The culture was centrifuged at 5,000 g for 30 min and the virus suspension obtained was subjected to ultrafiltration on a membrane of mol wt. 3 million and hole diameter 1,500 Angstrom. The virus suspension was centrifuged to remove insoluble particles, concentrated by circulating filtration and diluted in phosphate buffer. After repeating the purification step 3 times, the infection value of the obtained virus was 4-fold that of the unpurified virus solution. (6pp)

91s3/7/112 116 117 127-129 131 135 137 143 149 151-154 158 166 167 170

3/7/112

DIALOG(R)File 357:Derwent Biotechnology Abs

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093327 DBA Accession No.: 89-11318 PATENT

Production of antigen component for cattle leukemia virus vaccine - purification of antigen from cell culture infected with cattle leukemia virus

PATENT ASSIGNEE: Mitsui-Toatsu-Chem.; Mitsui-Pharm. 1989

PATENT NUMBER: JP 1125329 PATENT DATE: 890517 WPI ACCESSION NO.: 89-187891 (8926)

PRIORITY APPLIC. NO.: JP 87281759 APPLIC. DATE: 871107

NATIONAL APPLIC. NO.: JP 87281759 APPLIC. DATE: 871107

LANGUAGE: Japanese

ABSTRACT: A new method for preparation of a bovine leukemia virus (BLV) vaccine involves: (a) inactivation of crude BLV obtained from host cells infected with BLV, and (b) ultrafiltration of the solution containing the crude protein to give a concentrated fraction containing the purified protein. The vaccine retains its immunogenicity and is highly safe. In an example, fetal lamb kidney cells infected with BLV (FLK-BLV) were cultured at 37 deg under CO₂ in RPMI 1640 culture medium containing 10% fetal calf serum for 2-4 days, at a cell concentration of 1 million cells/ml. The resultant culture fluid was centrifuged at 2,000 rpm for precipitation of FLK-BLV. 0.1% Methanol was added to the supernatant. The mixture was shaken at 4 deg for 48 hr and was then subjected to ultrafiltration on a Pellicon Lab-cassette pore size 10,000 NMWL for 50-90-fold concentration. The concentrate was freeze-dried. The BLV vaccine was formulated by dissolving the powdered product in distilled water and addition of Freund's complete adjuvant. The vaccine was injected into cattle and the anti-BLV titer was determined periodically. The ELISA value was about 1 after 2 wk. (12pp)

3/7/116

DIALOG(R)File 357:Derwent Biotechnology Abs

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087321 DBA Accession No.: 89-05312 PATENT

Production of human B-lymphotropic virus in HSB-2 cell line - potential application of HBLV in diagnosis

PATENT ASSIGNEE: Electro-Nucleonics 1989

PATENT NUMBER: WO 8900599 PATENT DATE: 890126 WPI ACCESSION NO.: 89-054078 (8907)

PRIORITY APPLIC. NO.: US 72354 APPLIC. DATE: 870713

NATIONAL APPLIC. NO.: WO 88US2332 APPLIC. DATE: 880711

LANGUAGE: English

ABSTRACT: A new method of producing human B-lymphotropic virus (HBLV) involves culturing HBLV in the CCRF-HSB-2 (HSB-2) human T-lymphoblastoid cell line. More specifically, HSB-2 cells are mixed with HBLV-infected HSB-2 cells or with HBLV-containing supernatant collected from HBLV-infected HSB-2 cell culture. The infected HSB-2 cells (ATCC VR 2177) are then cultivated under conditions suitable for production of the virus. The uninfected cells are mixed with infected cells at a ratio of approximately 10:1. HBLV is harvested from the tissue culture and may be concentrated by high-speed centrifugation, ultrafiltration, or by precipitation methods. The infected HSB-2 cells provide a vehicle for large-scale production of HBLV and provides a source for in vitro cultivation for production of the virus. The virus can be characterized by protein purification, nucleic acid purification, infection studies in animals, and in vitro infection studies on other human target cells. The virus can be used in the development of human diagnostic tests to show the role of HBLV in lymphoproliferative, immune or neurological abnormalities e.g.

B-lymphocyte lymphoma. (13pp)

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DIALOG(R)File 357:Derwent Biotechnology Abs

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086781 DBA Accession No.: 89-04772

Employing ultrafiltration in the technology of avian-myeloblastosis virus

isolation - RNA-dependent DNA-polymerase large-scale preparation

AUTHOR: Azhernachev A K; Remyev Y V; Chuprunov V P; Colombet L V

CORPORATE SOURCE: All-Union Research Institute of Applied Microbiology;

Obolensk, Moscow Region, USSR.

JOURNAL: Biokhimiya (5, 1, 49-53) 1989

CODEN: BTKNEZ

LANGUAGE: Russian

ABSTRACT: The possibility of using hollow fibers for the concentration and purification of bird myeloblastosis virus under large-scale conditions in the process of manufacturing RNA-dependent DNA-polymerase (EC-2.7.7.7) was investigated. Virus-containing plasma from fowl was subjected to gel filtration on macroporous glass modified with polyvinylpyrrolidone (glass MPS-2000 VGH; pore size approx. 0.2 um) and then to ultrafiltration using hollow fibers made from polyacrylonitrile and aromatic polyamide (UPA-50). The virus concentration was determined according to ATP-ase (EC-3.6.1.3) activity. The hollow fibers retained almost all protein components of the plasma in addition to the virus particles, and prior to ultrafiltration the plasma proteins were removed by gel-filtration. The dynamics of gel filtration of virus-containing plasma on macroporous glass was studied. When the virus preparation was purified by gel filtration, the rate of ultrafiltration increased by 33% and there was a 2-3-fold reduction in the viscosity of the concentrate. (11 ref)

3/7/127

DIALOG(R)File 357:Derwent Biotechnology Abs

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075370 DBA Accession No.: 88-06219

Process technologies for in vitro production production of retro virus and monoclonal antibody for use as anticancer biologics - HTLV-I infected human cell culture and mouse hybridoma cell culture; product recovery (conference paper)

AUTHOR: Flickinger M C; Leherer III W B; Lee S M; Pickle D J; Hopkins

III R F

CORPORATE AFFILIATE: Program-Resour.

CORPORATE SOURCE: Institute for Advanced Studies in Biological Process

Technology, 1479 Gortner Ave., University of Minnesota, St. Paul, MN

55108, USA.

JOURNAL: Dev Ind Microbiol. (27, 87-99) 1987

CODEN: DIMCAL

LANGUAGE: English

ABSTRACT: 2 Processes at pilot-scale are described which allow efficient in vitro production of retro virus and monoclonal antibody (MAb) for application as tumor therapies. Human T-cell lymphoma virus type I (HTLV-I) was produced from HTLV-I shedding cells (HUT 102 B2 and C10/MJ-2) grown in low serum medium. Alternative methods for large-scale isolation of virus were evaluated such as continuous flow centrifugation (CFC), tangential flow ultrafiltration (TFU) and isopycnic binding, modified for contained cell removal and virus recovery. A total yield of 73 mg purified 24 kDa virus core protein was isolated, equivalent to 220 mg intact virus. A mouse-mouse hybridoma (producing MAb against human M14 melanoma 240 kDa glycoprotein/proteoglycan) was grown in submerged suspension culture in 50 l agitated vessels. Sub-lots containing secreted IgG1 were produced in 280 l quantities. The supernatant was concentrated 10-20-fold by TFU then further by protein A-Sepharose affinity column chromatography. Eluted fractions were concentrated to 15-20 mg protein/ml by 100 kDa TFU. (22 ref)

3/7/128

DIALOG(R)File 357:Derwent Biotechnology Abs

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074692 DBA Accession No.: 88-05541 PATENT

method for purification of rabic virus - useful for vaccine against rabies (US Equivalent)

PATENT ASSIGNEE: Chemo-Sero-Ther.Res.Inst. 1988

PATENT NUMBER: US 4725547 PATENT DATE: 880216 WPI ACCESSION NO.: 86-049659 (8608)

PRIORITY APPLIC. NO.: JP 84168226 APPLIC. DATE: 840810

NATIONAL APPLIC. NO.: US 764132 APPLIC. DATE: 850809

LANGUAGE: English

ABSTRACT: Rabic virus is purified by subjecting a solution of it to column chromatography using a sulfuric acid ester of cellulose or a crosslinked polysaccharide as a chromatographic gel. The ester is prepared by treating a gel of cellulose or crosslinked polysaccharide with a sulfating agent in an organic solvent. The virus solution is preferably harvested from a culture medium using a cell culture of chick embryo or by propagating rabies virus infected into the brains of mice. The virus is used to prepare an effective vaccine against rabies. In a typical procedure, chick embryo cells are inoculated with rabic virus and cultivation is performed at 35 deg for 5-7 days. Virus is harvested by membrane filtration and inactivated by treatment with beta-propiolactone at 37 deg for 60 min. The suspension is concentrated by ultrafiltration and ultra-high-speed centrifugation, and the precipitate is treated with NaCl-containing buffer (pH 7.1). Vaccine is obtained by conditioning and freeze-drying. (4pp)

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DIALOG(R)File 357:Derwent Biotechnology Abs

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074691 DBA Accession No.: 88-05540 PATENT

Method for purification of Japanese encephalitis virus - useful as vaccine

(US Equivalent)

PATENT ASSIGNEE: Chemo-Sero-Ther Res Inst. 1988

PATENT NUMBER: US 4725546 PATENT DATE: 880216 WP1 ACCESSION NO.:

86-049653 (8608)

PRIORITY APPLIC. NO.: JP 84167323 APPLIC. DATE: 840809

NATIONAL APPLIC. NO.: US 764130 APPLIC. DATE: 850809

LANGUAGE: English

ABSTRACT: Japanese encephalitis virus is purified by subjecting a solution of it to column chromatography using a sulfuric acid ester of cellulose or a crosslinked polysaccharide as a chromatographic gel. The ester is prepared by treating a gel of cellulose or crosslinked polysaccharide with a sulfating agent in an organic solvent. The virus preferably contains inactivated encephalitis virus or non-inactivated virus. The ester comprises crosslinked cellulose sulfate, crosslinked agarose sulfate, or crosslinked dextran sulfate. The virus is used for obtaining an effective vaccine against Japanese encephalitis. In a typical procedure, virus-containing material from mice brains is subjected to high-speed centrifugation. Protamine sulfate is added to the supernatant. Further high-speed centrifugation yields a supernatant to which activated charcoal is added. Membrane filtration gives a virus suspension which is inactivated using formalin and then subjected to ultrafiltration and ultra-high-speed centrifugation. The precipitate is suspended in phosphate-buffered NaCl solution, gelatine is added, and the bulk is diluted to give the vaccine. (4pp)

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DIALOG(R)File 357:Derwent Biotechnology Abs

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069811 DBA Accession No.: 88-00159

Production in Vero cells of an inactivated rabies vaccine from strain FRV/K for animal and human use - testing of antigenic potency and safety.

AUTHOR: El-Karamany R

CORPORATE SOURCE: Department of Virology, Public Health Laboratories, P.O.

Box 5540, 13056 Safat, Kuwait.

JOURNAL: Acta Virol. (31, 4, 321-28) 1987

CODEN: AVIRA2

LANGUAGE: English

ABSTRACT: A new concentrated and purified rabies vaccine was produced in Vero cells. 2 Rabies virus strains, the fixed rabies virus Pasteur (FRV) and Pitman Moore (PM) were adapted to Vero cells by 20 cycles of alternating passages in the brain of weaning mice. Intracerebral (i.c.) inoculation of weaning mice was followed by 17 and 20 serial passages

in Vero cells of RfV and PM strains, respectively. The adapted strains were designated as FRV/K and PM/K and had titers of 1,000,000 +/- 1.5 log (LD50/ml for i.c. inoculated mice) in several harvests taken from 1 infected cell culture. Pooled harvests were concentrated 20-fold by ultrafiltration and were tested as animal vaccine after inactivation with beta-propiolactone (BPL). The antigenic content of different strain FRV/K harvests was very high in comparison with that of strain PM/K and a reference tissue culture vaccine (RfV, Netherlands). In sheep, the antibody response induced by the FRV/K strain was very high: serum neutralizing index (NI) was over 4 within 40 days after the 2nd vaccine dose, whereas the vaccine preparation from PM/K gave an NI value of 2/3 and the reference vaccine 3.8. (16 ref)

3/7/135

DIALOG(R)File 357:Derwent Biotechnology Abs

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064557 DBA Accession No.: 87-08905 PATENT

Large scale production of rabies vaccine - by inoculation of rabies virus into VERO cell culture

PATENT ASSIGNEE: Wiktor T J 1987

PATENT NUMBER: US 4664912 PATENT DATE: 870512 WP1 ACCESSION NO.:

87-150273 (8721)

PRIORITY APPLIC. NO.: US 656762 APPLIC. DATE: 841001

NATIONAL APPLIC. NO.: US 656762 APPLIC. DATE: 841001

LANGUAGE: English

ABSTRACT: A process for the production of rabies vaccine comprises serial VERO cell culture immobilized on 1-10 mg/l microcarrier in a nutrient medium, each passage being carried out for 5-8 days at an agitation rate of not more than 40 rpm. The final passage is carried out in a culture vessel of at least 150 l volume. At the end of the final passage the nutrient medium is drawn off and replaced with a serum-free medium, and the VERO cells are inoculated with rabies virus and cultured at 35-37 deg, pH 7.4-7.8 at a partial oxygen pressure of 10-50%, 40 rpm. After at least 5 days the culture medium is removed, filtrated, ultrafiltrated to concentrate it 100-fold, treated with beta-propiolactone to inactivate it, and further purified by zonal centrifugation or chromatography. Preferably the microcarriers are separated from the cells during removal of the nutrient medium by addition of dilute protease, the infecting virus is Pitman-Moore PM 1.503-3 M strain, and the ultrafiltration cut off value is mol wt. 10,000-1 million. A highly purified, stable vaccine with high antigenic value of at least 2.5 U/ml is obtained. (6pp)

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DIALOG(R)File 357:Derwent Biotechnology Abs

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061453 DBA Accession No.: 87-05801 PATENT

Vaccine for bluetongue disease etc. using platinum compounds - for non-enveloped virus inactivation; virus preparation and purification from cell culture

PATENT ASSIGNEE: Univ.Calif. 1987

PATENT NUMBER: US 4645666 PATENT DATE: 870224 WPI ACCESSION NO.: 84-001367 (8401)

PRIORITY APPLIC. NO.: US 386469 APPLIC. DATE: 820608

NATIONAL APPLIC. NO.: US 386469 APPLIC. DATE: 820608

LANGUAGE: English

ABSTRACT: A vaccine against bluetongue virus (BTV) is prepared by inactivation of non-enveloped virus with cis-diamino chelated platinumous halide in the presence of a detergent. The viruses usually have a double-stranded genome, more particularly double-stranded RNA. The method may be applied to orbi virus, rota virus, picorna virus, reo virus, rhino virus, coxsackie virus etc. Particular viruses include bluetongue virus reovirus type 3, polio virus and Rous sarcoma virus. The virus is cultured in host cells in a suitable culture medium supplemented with amino acids, serum, antibiotics and buffer. The inoculated cells are incubated for 12-48 hr, and the virus is then harvested when 90% or more of the cells show cytopathic effects of infection. The cells are disrupted by e.g. sonication, and further purification is performed by e.g. ultrafiltration. The virus is then inactivated with the platinum compound and detergent, preferably using consecutive treatments. The detergent is preferably nonionic, e.g. Tween QS or Triton. (4pp)

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DIALOG(R)File 357:Derwent Biotechnology Abs

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046919 DBA Accession No.: 86-04767 PATENT

Oral vaccine production by inactivating virus in presence of protective compounds - from the culture medium, adding further stabilizer and then freeze-drying

PATENT ASSIGNEE: Lunghenkr.Tuberk.Forschungsinst. 1985

PATENT NUMBER: DD 229031 PATENT DATE: 851030 WPI ACCESSION NO.: 86-055952

(8609)

PRIORITY APPLIC. NO.: DD 269629 APPLIC. DATE: 841119

NATIONAL APPLIC. NO.: DD 269629 APPLIC. DATE: 841119

LANGUAGE: German

ABSTRACT: Production of oral vaccine comprises inactivating a virus in the presence of protective materials derived from the virus culture medium. Inactivation is by: (a) treatment with 1:15000 HCHO plus 9.5 kGy Co-60 gamma rays; (b) 1:5000 HCHO at 24 deg; (c) by incubation at 28 deg for up to 10 days; or (d) by treatment with e.g. UV light, microwaves or by splitting the virus. The inactivated virus, optionally after concentration by ultrafiltration, is then treated with an additional

protective colloid mixture (e.g. skim milk at 10-15 vol %) or with a simple stabilizer (e.g. dextran), and the resulting mixture is cooled to below 0 deg and freeze-dried. If the virus is adequately attenuated in active form, then the inactivation step can be omitted. The vaccines are useful in human or veterinary medicine, particularly to protect against influenza. The process minimizes loss of antigenic/immunogenic components, prevents contamination, and all the steps are simple to perform. The final vaccine requires no further purification. (4pp)

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DIALOG(R)File 357:Derwent Biotechnology Abs

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039441 DBA Accession No.: 85-10230 PATENT

Process for continuous culture of cells on a large scale - e.g. production of distemper virus using Vero cell culture

PATENT ASSIGNEE: Nippon-Zenyaku 1985

PATENT NUMBER: JP 60102187 (Kokai) PATENT DATE: 850606 WPI ACCESSION NO.: 85-174080 (8529)

PRIORITY APPLIC. NO.: JP 83208762 APPLIC. DATE: 831107

NATIONAL APPLIC. NO.: JP 83208762 APPLIC. DATE: 831107

LANGUAGE: Japanese

ABSTRACT: A process for the continuous culture of cells for production of a large amount of the latter is described. The cells are cultured in a circulating culture medium and separated out from the circulating culture broth. The cells may be infected with virus or may be used for the production of antibody with marrow cells, thymocytes or hybridoma cells etc. A microcarrier is also employed for the culture. The cells are separated by use of a molecular sieve or by ultrafiltration. In an example, Vero cells were precultured in a culture medium for 4 days. They were then added to a culture vessel. The precultured product was recovered by trypsin treatment and the cells were dispersed by collagenase treatment. The preculture was effected using a microcarrier for 2 days, and the mixture was transferred to a spinner-flask. Incubation was effected for 2 days in the presence of a microcarrier. The distemper virus was used to inoculate the cells, and continuous culture was effected for 2 wk. (4pp)

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DIALOG(R)File 357:Derwent Biotechnology Abs

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039168 DBA Accession No.: 85-09957 PATENT

Large-scale production of polio myelitis vaccine - with separate cultivation of virus in a medium on microcarriers; Vero cell culture

PATENT ASSIGNEE: Inst.Merieux 1985

PATENT NUMBER: US 4525349 PATENT DATE: 850625 WPI ACCESSION NO.: 85-171063 (8528)

PRIORITY APPLIC. NO.: US 335352 APPLIC. DATE: 811229

NATIONAL APPLIC. NO.: US 335352 APPLIC. DATE: 811229

LANGUAGE: English

ABSTRACT: The large-scale production of polio myelitis vaccine comprises the multiplication of a Vero cell strain from a cell stock by cultivation on microcarriers in a suspension in a liquid culture medium. The microcarriers are ball-shaped and are made of dextran polymers bearing grafted DEAE groups on their surfaces. Successive passages into increasing volumes of biogenerators are used, each for 6-8 days. The last passage is in a biogenerator with at least a 150 l tank. The medium contains serum and is removed at the end of the final passage and replaced with serum-free medium. The biogenerator of the last passage is inoculated with virus and allowed to develop at 35-37 deg and at pH 7.4 with a partial O₂ pressure of 10% with stirring. The medium is withdrawn, filtered and then concentrated by ultrafiltration. After gel filtration, the suspension is diluted with serum-free medium and inactivated. A stable vaccine containing types 1, 2 and 3 antigens in effective proportions can be produced, and the vaccine has a high antigenic value in a small volume. (6pp)

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DIALOG(R)File 357:Derwent Biotechnology Abs

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038532 DBA Accession No.: 85-09321

Ultrafiltration in the pharmaceutical industry - methods and use in biotechnology; a review

AUTHOR: Selin MM

CORPORATE SOURCE: All-Union Scientific-Research Institute of Blood Substitutes and Hormonal Preparations, Moscow, USSR.

JOURNAL: Khim.Farm.Zh. (19, 5, 573-83) 1985

CODEN: KHEZAN

LANGUAGE: Russian

ABSTRACT: Data in the literature are reviewed on selective membranes, the mechanism of selective membrane permeability, ultrafiltration devices, and the use of ultrafiltration for the separation of solutions of biologically-active substances. Reference is made to ultrafiltration membranes based on cellulose derivatives, polyacrylates, polyamides, polyvinyl chloride, polyesters, polysulfones, copolymers of N-vinylpyrrolidone and methylmethacrylate, and copolymers of vinyl chloride and acrylonitrile. The use of ultrafiltration for the purification and concentration of solutions of proteins, enzymes, viruses and antibiotics and for the purification and concentration of solutions of proteins, enzymes, viruses and antibiotics and for the preparation of vaccines and sera is considered. The use of ultrafiltration for the analysis of low mol wt. biologically active substances is discussed. Literature is cited concerning the determination of glucose and bilirubin in mixtures with hemoglobin and albumin. The concentration of penicillinase and trypsin and the

isolation of proteins with molecular masses of 1,000-100,000 are considered. (118 ref)

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DIALOG(R)File 357:Derwent Biotechnology Abs

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038443 DBA Accession No.: 85-09232

Hollow fiber cell culture systems for economical cell-product manufacturing - a review of the design operation and the biological aspects

AUTHOR: Hopkinson J

CORPORATE SOURCE: Director of Marketing, Filtration Products, for Amicon Corporation, Danvers, MA 01923, USA.

JOURNAL: Bio/Technology (3, 3, 225, 227-30) 1985

CODEN: 2049Y

LANGUAGE: English

ABSTRACT: Small, hollow, fiber cell culture units, modeled closely on the in vivo capillary system, have been designed and constructed. These were far more efficient than existing methods for the manufacture of monoclonal antibodies, growth factors, plasminogen-activators, interferons, viruses and tumor associated antigens. Fiber composition and structure and cartridge packing density and aspect ratio are important design parameters. In its most basic configuration the medium consists of culture cartridge, medium reservoir, recirculation pump and silicone tubing in a closed loop. The operation of the system the ultrafiltration layer lining the fiber lumen, and product collection are discussed. Biological aspects of the system include ideal environmental conditions and a steady cell state is created since, while cell division at a rapid rate ceases, the other metabolic functions continue at high levels for months. Purification is facilitated by the accumulation of a highly concentrated, uncontaminated, solution in the extra-capillary chamber. Manufacturing aspects are summarized and a cost-comparison of monoclonal antibody production made. (24 ref)

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DIALOG(R)File 357:Derwent Biotechnology Abs

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037681 DBA Accession No.: 85-08470

Production of human T-cell lymphoma virus type I (HTLV-I) by large-scale suspension culture - batch culture scale-up and product recovery (conference abstract)

AUTHOR: Leberth III W B, Pickle D J, Roberts V A, Lufriu I, Flickinger M C

CORPORATE AFFILIATE: Program-Resources

CORPORATE SOURCE: Program Resources, Inc., NCI-Fredrick Cancer Research Facility, Fermentation Program, P O. Box B, Frederick, MD 27101, USA. JOURNAL: In Vitro (21, 3, Pt.2, 17A) 1985

CODEN: 4587E

LANGUAGE: English

ABSTRACT: Human T-cell lymphoma virus, type I (HTLV-I) was produced in large-scale suspension cultures under P3 containment conditions. A batch process was scaled up to the 200 l scale using Rushton impeller agitation at low tip velocity and direct gas sparging in 3:1 (H:D) bottom drive stainless steel fermentors. Seed cultures of virus-production cell lines were either adapted for growth at reduced serum (FBS) level in RPMI-1640 medium or were rapidly weaned to reduced FBS levels over 3 passages immediately prior to inoculation into production fermentors. Large-scale techniques for contained processing of 2000X concentrated HTLV-I suspensions included cell removal by centrifugation or microporous ultrafiltration, concentration of virus-rich supernatants by ultrafiltration prior to banding, and both single and double bandings on sucrose gradients in a large scale continuous flow ultracentrifuge. Overlapping of scale-up, production, and processing phases allowed for the production of 200 l of virus-rich supernatant in 14 day cycles, resulting in a total yield of 73 mg of HTLV-I core protein over a 14 month period. This quantity represents 200 mg of intact HTLV-I. (0 ref)

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DIALOG(R)File 357:Derwent Biotechnology Abs

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031291 DBA Accession No.: 85-02080

New frontiers in membrane technology and chromatography: applications for biotechnology - the use of bioengineering in industry

AUTHOR: Warren D C

CORPORATE SOURCE: Department of Chemistry, Houston Baptist University, 7502 Fondren Rd., Houston, Tex 77074-3298, U.S.A.

JOURNAL: Anal.Chem. (56, 14, 1528A-40A,1543A-44A) 1984

CODEN: ANCHAM

LANGUAGE: English

ABSTRACT: The application of bioengineering to solving the problems of industry is discussed. The use of industrial microorganisms in batch and continuous processes is briefly considered. Biotechnology instrumentation is discussed, with reference to protein-amino acid analyzers. Amino acid analysis and protein sequencing are used in tandem with the oligonucleotide synthesizer, and the synthesis of nucleic acids-nucleotides is considered. The importance of separation or purification in the production of biotechnological and genetically engineered products in general is stressed, and membrane and chromatographic methods are evaluated. Protein purification design is outlined, and the paper deals with membrane separation technology. Consideration is given to membrane configuration, microporous filtration, ultrafiltration, reverse osmosis, dialysis and electro dialysis, gas separations and the use of supported liquid

membranes. Separations are important in the areas of cell growth, separation of the product from biomass, product purification, virus harvesting, cell recycle, process chromatography, fermentation cell harvesting and microstructure surface chemistry. (0 ref)

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DIALOG(R)File 357:Derwent Biotechnology Abs

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011033 DBA Accession No.: 83-02880

Concentration and analysis of labile viruses by hollow fibre ultrafiltration and analysis of labile viruses by hollow fibre ultrafiltration and ultracentrifugation - applied to rubella and human respiratory syncytial viruses

AUTHOR: Trudel M; Trepanier P; Paymen P

CORPORATE SOURCE: Institut Armand-Frappier, Universite du Quebec, Centre de Recherche en Virologie, Laval-des-Rapides, Laval, Quebec, Canada H7N 4Z3.

JOURNAL: Process Biochem. (18, 1, 2-4, 9) 1983

CODEN: 7950W

LANGUAGE: English

ABSTRACT: Hollow fibre ultrafiltration proved a very successful method for the concentration of labile enveloped viruses. Rubella virus strain M-33 ATCC VR-315 was grown in Vero cells ATCC, CCL1, B1, which were produced in a tissue culture propagator. Viral supernatants showing haemagglutinating activity were collected and concentrated by hollow fibre ultrafiltration. This was carried out using alternatively the DC-10 and CH-4 systems in 4.5 hr. The combined recovery of 81.2% for a 2500 fold concentration. Only 12.1% of the protein content was found in the concentrate. Similarly 5 l of human respiratory syncytial virus suspension were concentrated using the Ch-4 system, with nearly 95% recovery of infectious units. The use of an Airfuge ultracentrifuge to separate viral cores allows the pelleting of rubella and human respiratory syncytial viruses in a short time. Rate zonal density centrifugation has also been applied to the screening of 125I labelled mouse monoclonal antibodies with specific binding affinity for the surface proteins. (14 ref)

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009518 DBA Accession No.: 83-03918

Rabies vaccine prepared from the virus grown in Japanese quail embryo cell cultures - concentrated by ultrafiltration and inactivated with beta-propiolactone

AUTHOR: Bektemirova M S; Pille E R; Matevosyan K S; Nagieva F G

CORPORATE SOURCE: Research Institute for Viral Preparations, 109088 Moscow, USSR.

JOURNAL: Acta Virol. (27, 1, 59-64) 1983

CODEN: AVIRA2

LANGUAGE: English

ABSTRACT: Fixed rabies virus strain MNIVP-74 was grown in Japanese quail embryo cell cultures, concentrated by ultrafiltration and inactivated with beta-propiolactone. Prior to inactivation, the infectious titer of the MNIVP-74 virus grown in JQE cell culture was 5.75-6.75 LD50/ml. Virus concentration 10 to 30 fold resulted in a rise of its titer by 1.0-1.25 log LD50/ml. The content of the protein prior to the addition of the stabilizer (human serum albumin) was less than 150 ug/ml. The regimen of beta-propiolactone treatment resulted in its reliable inactivation. Live virus was not present in the vaccine. The concentrated cell culture-grown vaccine was markedly immunogenic and sufficiently thermostable. Intermittent dosage of human volunteers resulted in more intensive and longer antibody production than those injected daily. (9 ref)

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DIALOG(R)File 357:Derwent Biotechnology Abs

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002490 DBA Accession No.: 82-01490 PATENT

Deactivated Sendai virus vaccine - hemagglutinating virus of Japan inoculated in chicken eggs followed by treatment with nonionic surfactant and organic solvent

PATENT ASSIGNEE: Takeda 1982

PATENT NUMBER: JP 57095917 PATENT DATE: 820615 WPI ACCESSION NO.:

82-60700E (6029)

PRIORITY APPLIC. NO.: JP 80171795 APPLIC. DATE: 801204

NATIONAL APPLIC. NO.: JP 80171795 APPLIC. DATE: 801204

LANGUAGE: Japanese

ABSTRACT: Deactivated Sendai virus vaccine may be produced by treating a pellet of Sendai virus with nonionic surfactant and organic solvent not miscible with water. During this procedure it is ensured that no salt is present. An example is cited where Sendai virus (Hemagglutinating virus of Japan; HJV) was inoculated into the chorioallantoic cavity of growing chicken eggs. After 3 days the eggs were subjected to cold treatment (4 deg for 6-18 hr). The shell was opened and the chorioallantoic cavity liquor was pooled. Phosphoric acid, sodium chloride solution, and kanamycin were added. The mixture was concentrated by fractionary centrifugation. Unwanted cell debris was removed by a preliminary centrifugal step. The Pellet of HJV was then obtained by ultrafiltration. Following extraction with ethyl ether, Glucose and Kanamycin were added to the inactivated HJV and the mixture was freeze dried and vacuum sealed. (5pp)

? ds

Set Items Description
S1 3253 ULTRAFIL.T?

S2 22820 VIRUS OR VIRUSES

S3 170 S1 AND S2

? s viscous or viscosity

595 VISCIOUS

1633 VISCOSITY

S4 2054 VISCIOUS OR VISCOSITY

? s s1 and s4

3253 S1

2054 S4

S5 63 S1 AND S4

? 1 s5/7/19 27-29 35 38 43 50 57

5/7/19

DIALOG(R)File 357:Derwent Biotechnology Abs

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136915 DBA Accession No.: 92-09407

Benzon nuclease. A new endonuclease to eliminate interfering nucleic acids - Serratia marcescens recombinant benzonase produced by plasmid pNUC1 expression in Escherichia coli; characterization and application in RNA and DNA contaminant removal

AUTHOR: Anon

CORPORATE AFFILIATE: Merck-USA

CORPORATE SOURCE: (Publ.Address) Teknoscience Srl, via Gioberti 1, 20123

Milan, Italy.

JOURNAL: Chim. Oggi (10, 4, 49-51) 1992

CODEN: 3127E

LANGUAGE: English

ABSTRACT: Benzon nuclease (benzonase, (I)), a recombinant endonuclease expressed in Escherichia coli carrying plasmid pNUC1 (encoding a Serratia marcescens nuclease), was characterized. (I) degrades all types of DNA and RNA (double-stranded, single-stranded, linear, circular, and supercoiled) into 3-5 bp oligonucleotides. The activity of (I) is over 90% at 400,000 U/mg protein, and over 99% at 1 million U/mg protein, and protease activity is low (less than 100,000 U/mg/100,000 U. (I) activity is optimal at pH 7.8-9.2 (stable at pH 6-10) and 37 deg (stable at 0-42 deg). It has a pl of 6.85 and a mol.wt. of 30,000 (SDS-PAGE). (I) is stable in cell lysates saturated with phenol, toluene or chloroform, and in the presence of ionic or non-ionic surfactants, denaturing agents, reducing agents or urea. Increased activity occurred with 1% Triton X-100, 4 uM urea or 1 mM Mg2+, but inhibition occurred with monovalent cations. (I) may be used in downstream processing of cell lysates prior to pipetting, ultrafiltration or centrifugation, in order to reduce viscosity without causing shear, and in DNA/RNA removal from waste-water, culture medium, etc. (0 ref)

5/7/27

DIALOG(R)File 357:Derwent Biotechnology Abs

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098501 DBA Accession No.: 90-01192

Use of cross-flow techniques in biotechnology - cross-flow filtration application

AUTHOR: Faust T, +Kopf K H

CORPORATE AFFILIATE: BASF

CORPORATE SOURCE: Giltbergasse 9, 6733 Hassloch, Germany.

JOURNAL: Chem.Eng. Tech. (61, 6, 459-68) 1989

CODEN: CITEAH

LANGUAGE: German

ABSTRACT: Problems encountered in the development of micro and ultrafiltration processing in biotechnology are discussed regarding data collection for definition of processing stages, solid/liquid separation, concentration of solutions, fractionation of products, diafiltration, description of product specification and economic aspects. Product properties requiring checking include pH, viscosity, presence of proteins, crystals and other particles and microorganisms. Requirements for the membrane and its containing equipment involve sterilization, cleaning-in-place and suitable flexibility and serviceability. Once the membrane has been selected, laboratory trials should include construction of the test equipment, collection of data, anti-fouling techniques and membrane conditioning. (13 ref)

5/7/28

DIALOG(R)File 357:Derwent Biotechnology Abs

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097266 DBA Accession No.: 89-15257

Affinity ultrafiltration for purifying specialty chemicals - trypsin, urokinase, antithrombin-III and heparin purification (conference paper)

AUTHOR: Luong J H T; Maile K B; Nguyen A L; Mulchandani A

CORPORATE SOURCE: National Research Council of Canada, Biotechnology

Research Institute, Montreal, H4P 2R2, Canada.

JOURNAL: Carbiocon 1988 (Biotechnol Res Appl., 78-93) 1988

CODEN: 9999X

LANGUAGE: English

ABSTRACT: Affinity ultrafiltration combines affinity interactions and membrane separation. To test this type of system, batch and continuous processes were developed for purification of trypsin (EC-3.4.21.4) from a trypsin-chymotrypsin (EC-3.4.21.1) mixture, using a newly synthesized water-soluble high-mol wt. polymer bearing m-aminobenzamide, a strong trypsin-inhibitor. A mathematical model was developed to describe the behavior of an affinity ultrafiltration process. The high resolution and recovery possible with affinity ultrafiltration, with its capability for processing unclarified and viscous liquids, have given a large impetus to further development of its application. The technique may be applied for purification of biochemical compounds from the

liquid immediately after completion of fermentation. Affinity ultrafiltration has been applied for purification of specialty chemicals such as urokinase (EC-3.4.21.31), antithrombin-III and heparin. (4 ref)

5/7/29

DIALOG(R)File 357:Derwent Biotechnology Abs

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090645 DBA Accession No.: 89-08636

Harvesting and disruption of cells of recombinant *E. coli* in a continuous process for recombinant protein production, recovery and purification - (conference abstract)

AUTHOR: Robinson C W; +Glick B R; Sauer T; Wood D

CORPORATE SOURCE: Department of Biology, University of Waterloo, Waterloo,

Ontario, Canada N2L 3G1.

JOURNAL: Eur Congr Biotechnol. (Vol.2, 627) 1987

CODEN: 9999X

LANGUAGE: English

ABSTRACT: An integrated, multistage, continuous process for the production, recovery and purification of recombinant proteins was investigated. Biomass is produced in a 2-stage continuous loop fermentor, and following maximum gene expression, cells are continuously harvested by cross-flow microfiltration and subjected to disruption. The homogenizer effluent is then treated by either enzymatic (DNA-ase) or mechanical (ultrasonic) means in order to reduce viscosity and enhance the subsequent ultrafiltration step. The effects of microfiltration operating conditions (tangential shear rate, transmembrane pressure drop, cell concentration, membrane type, fermentation antifoam) on the permeation flux and retentate cell concentration were examined for recombinant *Escherichia coli* cells producing phage T4 DNA-ligase. The effects of disruption conditions on percentage disruption and DNA-ligase release and the effect of viscosity reduction and other relevant ultrafiltration operating variables on the prefractionation recovery of active enzyme were also examined. Implications for recovery of other intracellular recombinant products were presented. (2 ref)

5/7/35

DIALOG(R)File 357:Derwent Biotechnology Abs

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086781 DBA Accession No.: 89-04772

Employing ultrafiltration in the technology of avian-myeloblastosis virus isolation - RNA-dependent DNA-polymerase large-scale preparation

AUTHOR: Azharnachev A K; Remyev Y V; Chuprunov V P; Colombei L V

CORPORATE SOURCE: All-Union Research Institute of Applied Microbiology,

Obolensk, Moscow Region, USSR.

JOURNAL: Biokhimiya (5, 1, 49-53) 1989

CODEN: BTKNEZ

LANGUAGE: Russian

ABSTRACT: The possibility of using hollow fibers for the concentration and purification of bird myeloblastosis virus under large-scale conditions in the process of manufacturing RNA-dependent DNA-polymerase (EC-2.7.7.7) was investigated. Virus-containing plasma from fowl was subjected to gel filtration on macroporous glass modified with polyvinylpyrrolidone (glass MPS-2000 VGH; pore size approx. 0.2 um) and then to ultrafiltration using hollow fibers made from polyacrylonitrile and aromatic polyamide (UPA-50). The virus concentration was determined according to ATP-ase (EC-3.6.1.3) activity. The hollow fibers retained almost all protein components of the plasma in addition to the virus particles, and prior to ultrafiltration the plasma proteins were removed by gel-filtration. The dynamics of gel filtration of virus-containing plasma on macroporous glass was studied. When the virus preparation was purified by gel filtration, the rate of ultrafiltration increased by 33% and there was a 2-3-fold reduction in the viscosity of the concentrate. (11 ref)

5/7/38

DIALOG(R)File 357:Derwent Biotechnology Abs

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083920 DBA Accession No.: 89-01911

Depyrogenation of pharmaceutical solutions by ultrafiltration - factors influencing choice of system

AUTHOR: Wolber P; Dosmar M

CORPORATE AFFILIATE: Sartorius

CORPORATE SOURCE: (Pub. address) Australian Industrial Publishers Pty Ltd, 2 Wilford Avenue, P.O. Box 8, Cowandilla 5033, Australia.

JOURNAL: Aust.J.Biotechnol. (2, 1, 59-64) 1988

CODEN: 1605M

LANGUAGE: English

ABSTRACT: The following criteria must be considered in the validation process for ultrafiltration systems with the intention of depyrogenating pharmaceutical solutions: (1) biological safety; (2) level of extractables; (3) product compatibility; (4) membrane integrity; (5) pyrogen challenge; (6) system and membrane selection; (7) cleaning and depyrogenation and (8) sanitization/sterilization. The aspects unique to ultrafiltration are discussed. Pyrogen removal is influenced by the chemical properties of the fluid, the physical and chemical properties of the membrane, the physical properties and dynamics of the system, the aggregation state of the pyrogens, the mechanism of pyrogen removal, the concentration of the pyrogens and the volume and residue time. Since factors like pH, temp., viscosity and chemical components can influence the removal of pyrogens, the characterization of the membrane by the filter manufacturer facilitates in the membrane selection and validation process. The system must be able to be depyrogenated, sanitized, regenerated, must not react with

the product or pyrogens, and must be integrity testable. (25 ref)

5/7/43

DIALOG(R)File 357:Derwent Biotechnology Abs

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066062 DBA Accession No.: 87-10410 PATENT

Enzyme immobilized membrane - for use as ultrafiltration membrane reactor

PATENT ASSIGNEE: Nitto-Electric 1987

PATENT NUMBER: JP 62118888 (Kokai) PATENT DATE: 870530

WPI ACCESSION NO.: 87-189056 (8727)

PRIORITY APPLIC. NO.: JP 85259537 APPLIC. DATE: 851118

NATIONAL APPLIC. NO.: JP 85259537 APPLIC. DATE: 851118

LANGUAGE: Japanese

ABSTRACT: An immobilized enzyme membrane is prepared by (a) dehydration-condensation of 1,2,3,4-butane-tetracarboxylic acid (or its anhydride) and diamines, (b) mixing the thus obtained polyimide and polysulfone, (c) processing the mixture in an ultrafiltration membrane, and (d) immobilizing enzyme to the membrane through the carboxyl group of the polyimide. The polyimide has an average mol.wt. of 10,000-120,000 (preferably 30,000-80,000) and its intrinsic viscosity is 0.50-1.00 (preferably 0.6-0.85) in N-methylpyrrolidone solution at 30 deg. The polysulfone has a mol.wt. of 20,000-100,000 (preferably 30,000-60,000) and an intrinsic viscosity of 0.2-1.2 (preferably 0.4-0.8). The polyimide and polysulfone are used in a wt. ratio of 100:1-20. The support shows excellent thermal resistance and mechanical strength. Ultrafiltration membranes can be prepared containing large amounts of enzyme of high activity, for use in reactions in which the product is separated continuously. (6pp)

5/7/50

DIALOG(R)File 357:Derwent Biotechnology Abs

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047197 DBA Accession No.: 86-05045 PATENT

Enzyme concentration - by ultrafiltration

PATENT ASSIGNEE: Toyo-Soda 1986

PATENT NUMBER: JP 61012284 (Kokai) PATENT DATE: 860120

WPI ACCESSION NO.: 86-059593 (8609)

PRIORITY APPLIC. NO.: JP 84130886 APPLIC. DATE: 840627

NATIONAL APPLIC. NO.: JP 84130886 APPLIC. DATE: 840627

LANGUAGE: Japanese

ABSTRACT: A process is described for the processing of enzyme solutions and comprises concentration by ultrafiltration. In the 1st step, enzyme is allowed to pass through the ultrafiltration membrane. This is followed by ultrafiltration using a membrane which retains the enzyme. By using this process, difficulties arising due to filter clogging or increased viscosity of the enzyme solution are resolved. (3pp)

5/7/57

DIALOG(R)File 357:Derwent Biotechnology Abs

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022658 DBA Accession No.: 84-05933

Membrane filtration in biotechnology - industrial application of
ultrafiltration and reverse osmosis

AUTHOR: Sassero S

CORPORATE SOURCE: (Publ. Address) Konradin-Verlag Robert Kohlhammer GmbH,

Postfach 1380, 7022 Leinfelden-Echterdingen 1, Germany.

JOURNAL: Chem.Anlagen Verfahren (17, 4, 99-100) 1984

CODEN: CHAVBZ

LANGUAGE: German

ABSTRACT: Semi-permeable membranes are considered for the separation, purification and concentration of bio-materials using physical methods of separation. Industrial-scale reverse osmosis and ultrafiltration modules are described. The key applications of these devices are in the production of enzymes, glucose syrup, polysaccharides, protein hydrolyzates and acetic acid, but sterile filtration and the isolation of the pure D and L forms of amino acids are also considered. Xanthan solutions with a high viscosity is difficult to handle using ultrafiltration, but solutions in the range 100-4000 cP can be concentrated. (0 ref)

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04aug98 09:36:46 User208669 Session D1234.4

\$5.25 1.000 DialUnits File357

\$0.00 63 Type(s) in Format 6

\$18.00 9 Type(s) in Format 7

\$18.00 72 Types

\$23.25 Estimated cost File357

\$23.25 Estimated cost this search

\$23.25 Estimated total session cost 1.000 DialUnits

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23sep98 15:16:48 User208669 Session D1291.1

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\$0.14 Estimated total session cost 0.042 DialUnits

File 351:DERWENT WPI 1963-1998/UD=9837,UP=9834,UM=9832

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DIALOG(R)File 351:DERWENT WPI

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011176326

WPI Acc No: 97-154251/199714

XRAM Acc No: C97-049360

Purification of viruses for vaccine prodn. - using anion and cation exchange

chromatography, esp. useful for rabies, Japanese encephalitis or influenza
Patent Assignee: PASTEUR MERIEUX SERUMS & VACCINS (INMR); PASTEUR MERIEUX

SERUMS & VACCINS SA (INMR)

Inventor: FANGET B; FRANON A; FRANCON A

Number of Countries: 072 Number of Patents: 004

Patent Family:

Patent No Kind Date Week

WO 9706243 A1 19970220 199714 B

FR 2737730 A1 19970214 199716

AU 9664964 A 19970305 199726

EP 848752 A1 19980624 199829

Local Applications (No Type Date): WO 96FR1064 A 19960708; FR 959851 A

19950810; AU 9664964 A 19960708; EP 96924954 A 19960708; WO 96FR1064 A

19960708

Priority Applications (No Type Date): FR 959851 A 19950810

Abstract (Basic): WO 9706243 A

Protein viruses and cellular DNA, obtd. from a cell culture, are sepd. from DNA and proteins by ion exchange chromatography with at least 1 stage using an anion exchange resin and at least 1 stage using a cation exchange resin.

USE - The process is especially suitable for purifying viruses used in vaccine preps, esp for rabies, Japanese encephalitis or influenza (claimed).

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1/27/3

DIALOG(R)File 351:DERWENT WPI

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011167451

WPI Acc No: 97-145376/199713

XRAM Acc No: C97-046388

Large scale prodn. of vaccine against Japanese encephalitis in cultured cell lines - provides pure vaccine of low cellular DNA content, comprises harvesting virus-contg. supernatant from cell cultures, opt. several times from same cells

Patent Assignee: PASTEUR MERIEUX SERUMS & VACCINS (INMR); PASTEUR MERIEUX

SERUMS & VACCINS SA (INMR)

Inventor: FANGET B; FRANON A; HEIMENDINGER P; FRANCON A

Number of Countries: 072 Number of Patents: 005

Patent Family:

Patent No Kind Date Week

WO 9704803 A1 19970213 199713 B

FR 2737412 A1 19970207 199715

AU 9667041 A 19970226 199725

FR 2746411 A1 19970926 199746
EP 841942 A1 19980520 199824

Local Applications (No Type Date): WO 96FR1195 A 19960729; FR 959374 A
19950801; AU 9667041 A 19960729; FR 963638 A 19960322; EP 96927102 A
19960729; WO 96FR1195 A 19960729

Priority Applications (No Type Date): FR 963638 A 19960322; FR 959374 A
19950801

Abstract (Basic): WO 9704803 A

Large scale prodn. of vaccine against Japanese encephalitis
comprises: (a) inoculating cultured cells of a cell line with Japanese
encephalitis virus (JEV) in the presence of viral multiplication
medium; (b) propagating and multiplying JEV in the cells; (c) recovering
the medium which comprises a suspension of virus produced by the
cells; (d) purifying the viral suspension by at least 1 of ion-exchange
chromatography and gel permeation, and (e) forming the virus suspension
into a pharmaceutical compsn. to ensure its preservation until use.

Also claimed is the vaccine produced as above which contains <100

pg/dose DNA.

ADVANTAGE - This process is rapid, reliable and economic and
produces a very pure vaccine in good yields (several harvests of virus
can be taken from the same culture). The vaccine is free of viral
contaminants and suitable for systemic admin.

Dwg 0/0

1/27/4

DIALOG(R)File 351:DERWENT WPI

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009848273

WPI Acc No: 94-128129/199416

XRAM Acc No: C94-058997

Hepatitis A virus antigen prodn. from infected cell lysate - by anion
exchange chromatography and gel filtration in presence of detergent,
useful for making vaccines.

Patent Assignee: PASTEUR MERIEUX SERUMS & VACCINS (INMR); PASTEUR
MERIEUX

SERUMS & VACCINS SA (INMR)

Inventor: FANGET B; FRANCON A

Number of Countries: 019 Number of Patents: 005

Patent Family:

Patent No Kind Date Week

EP 593339 A1 19940420 199416 B

FR 2696748 A1 19940415 199418

CA 2108292 A 19940415 199426

JP 6279317 A 19941004 199444

US 5731187 A 19980324 199819

Local Applications (No Type Date): EP 93402469 A 19931007; FR 9212285 A
19921014; CA 2108292 A 19931013; JP 93280500 A 19931014; US 93136580 A

19931013

Priority Applications (No Type Date): FR 9212285 A 19921014

Abstract (Basic): EP 593339 A

Prodn. of antigens (Ag), or vaccines, from hepatitis A (HA)
comprises (1) growing HA virus in competent cells; (2) lysing infected
cells; (3) recovering supernatant and (4) purification by
chromatography on an anionic exchange support and be gel filtration.
The new feature is that purification is carried out in presence of a
detergent (A) and chromatography is under conditions that cause
retention of virions and viral capsids (which are subsequently eluted).
Pref. the detergent is Tween 80 at a conc. of 0.001-5 (esp. 0.1%).

USE/ADVANTAGE - The isolated Ag are inactivated then absorbed onto
Al(OH)₃ to produce a vaccine. (A) prevents absorption of capsids and
virions, and eliminates the need for extraction steps required in known
processes. After simple filtration of the lysate, a single
chromatography step is sufficient to remove contaminating proteins, and
nucleic acids (which are not retained).

Dwg. 0/0

Abstract (Equivalent): US 5731187 A

Prodn. of antigens (Ag), or vaccines, from hepatitis A (HA)
comprises (1) growing HA virus in competent cells; (2) lysing infected
cells; (3) recovering supernatant and (4) purification by
chromatography on an anionic exchange support and be gel filtration.
The new feature is that purification is carried out in presence of a
detergent (A) and chromatography is under conditions that cause
retention of virions and viral capsids (which are subsequently eluted).
Pref. the detergent is Tween 80 at a conc. of 0.001-5 (esp. 0.1%).

USE/ADVANTAGE - The isolated Ag are inactivated then absorbed onto
Al(OH)₃ to produce a vaccine. (A) prevents absorption of capsids and
virions, and eliminates the need for extraction steps required in known
processes. After simple filtration of the lysate, a single
chromatography step is sufficient to remove contaminating proteins, and
nucleic acids (which are not retained).

Dwg. 0/0

1/27/5

DIALOG(R)File 351:DERWENT WPI

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007150276

WPI Acc No: 87-150273/198721

XRAM Acc No: C87-062687

Large scale prodn. of rabies vaccine - with inoculation of virus into
large scale cell stock of Vero cell strain

Patent Assignee: WIKTOR T J (WIKT-J)

Inventor: FANGET B J; FOURNIER P; MONTAGNON B J

Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No Kind Date Week
 US 4664912 A 19870512 198721 B
 Local Applications (No Type Date): US 84656762 A 19841001
 Priority Applications (No Type Date): US 84656762 A 19841001
 Abstract (Basic): US 4664912 A

A process for the large-scale prodn. of rabies vaccine comprises (a) successively passing into biogenerators of increasing vol. a cell stock comprising a VERO cell strain and a liq. nutritive medium contg. serum, and having suspended therein microcarriers present in an amt. 1 to 10 3/4 of liq. nutritive medium, each passage being carried out with stirring at a rate not greater than 40 rpm and for 5 to 8 days, the last of the passages being carried out in a biogenerator having a vol. of at least 150 (b) drawing off the liq. nutritive medium at the end of the final passage and replacing with a serum-free liq. nutritive medium, (c) including the cell stock in the last passage biogenerator with virus and allowing the virus to develop at a temp. 35-37 deg. C at a pH of 7.4 to 7.8 and at a partial oxygen pressure of about 10-50 % while stirring at a rate not greater than 40 rpm, (d) culturing the virus for at least 5 days, (e) withdrawing the liq. suspension of cultured virus, (f) filtering the withdrawn liq. suspension, (g) ultrafiltering the filtered liq. suspension to concentrate the same at least 100 times, (h) inactivating the concn. suspension with beta-propiolactone and (i) purifying the inactivated suspension by zonal centrifugation or chromatography.

1/27/6

DIALOG(R)File 351:DERWENT WPI
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 004344185

WPI Acc No: 85-171063/198528
 XRAM Acc No: C85-074816

Large scale prodn. of poliomyelitis vaccine - with separate cultivation of viruses in medium on micro-carriers
 Patent Assignee: INST MERIEUX (INMR)
 Inventor: FANGET B J C; MONTAGNON B J
 Number of Countries: 002 Number of Patents: 002
 Patent Family:

Patent No Kind Date Week
 US 4525349 A 19850625 198528 B
 CA 1203170 A 19860415 198619
 Local Applications (No Type Date): US 81335352 A 19811229
 Priority Applications (No Type Date): US 81335352 A 19811229
 Abstract (Basic): US 4525349 A

Large-Scale prodn. of poliomyelitis vaccine comprises separately, for each type of virus used, (a) multiplication of a VERO cell strain from a cell stock by cultivation on microcarriers in suspn. in a liquid nutritive medium. The microcarriers are ball shaped with average dia.

of 50-300 microns in the dry state and with density slightly over 1. They are made of dextran polymers bearing grafted diethylaminoethyl gps. on their surfaces. The concn. of microcarriers is 1-5 g/l liquid medium. Successive passages into increasing vols. of biogenerators are used, each for 6-8 days. The last passage is in a biogenerator with at least 1 l 50 l tank. The liquid medium contains serum. It is stirred at up to 40 r.p.m. Liquid medium is removed at the end of the final passage and replaced by serum-free medium. The biogenerator of the last passage is inoculated with virus, and it is allowed to develop at 35-7 deg. C and at pH 7.4 with a partial O2 pressure of about 10% and with stirring at up to 40 r.p.m.; (b) withdrawal of liquid medium after the culture; (c) filtration of the medium then concn. by ultrafiltration to at least 150-fold; (d) gel filtration of the concn. suspn. followed by ion-exchange chromatography; (e) dilution of the resulting concd. suspn. with a serum-free medium; (f) inactivation of the suspn.; and (g) mixing of the suspns. of the various types used, and prepn. of the individual dosages.

USE/ADVANTAGE - The large-scale prodn. is economic and easy to carry out. A stable vaccine contg. types 1, 2 and 3 antigens in effective proportions can be produced. The vaccine obd. may have a high antigenic value in a small vol. (6pp Dwg.No 0/0)

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DIALINDEX(R)

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138 5: BIOSIS PREVIEWS(R)_1969-1998/JUL W4
1 6: NTIS_64-1998/Aug W5
1 9: Business & Industry(R)_Jul_1994-1998/Aug 04
2 15: ABI/INFORM(R)_1971-1998/Jul W4
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69 73: EMBASE_1974-1998/Aug W1
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1 108: Aerospace Database_1962-1998/July

Examined 50 files
17 144: Pascal_1973-1998/Jun
12 148: IAC Trade & Industry Database_1976-1998/Aug 04
116 155: MEDLINE(R)_1966-1998/Sep W4
18 156: Toxline(R)_1965-1998/Jul
2 161: Occ.Saf.& Hth_1973-1998/Q2
2 187: F-D-C Reports_1987-1998/Jul W4
1 211 IAC Newsearch(TM)_1997-1998/Aug 04
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6 265: FEDRIP_1998/Jun

1 305: Analytical Abstracts_1980-1998/Aug

2 315: ChemEng & Biotec Abs_1970-1998/Aug

1 319: Chem Bus NewsBase_1984-1998/Jul W4

5 340: CLAIMS(R)/US Patent_1950-98/Jul 28

Examined 100 files

1 345: Impadoc/Fam.& Legal Stat_1998/UD=9829

383 348: EUROPEAN PATENTS_1978-1998/Jul W3-

18 351: DERWENT WPI_1963-1998/UD=9830;UP=9827;UM=9825

1 353: AP/PAT_1964-1998/Jul W4

1 376: Derwent Drug File_1964-1982

25 377: Derwent Drug File_1983-1998/Jul W4

5 429: Adis Newsletters(Archive)_1982-1998/Jul 06

2 434: SciSearch(R) Cited Ref Sci_1974-1989/Dec

3 442: AMA Journals_1982-1998/Jul W4

8 444: New England Journal of Med_1985-1998/Aug W1

5 457: The Lancet_1986-1998/Jul W4

1 624: McGraw-Hill Publications_1985-1998/Jul 30

3 635: Business Dateline(R)_1985-1998/Jul W4

10 636: IAC Newsletter DB(TM)_1987-1998/Aug 04

13 652: US Patents Fulltext_1971-1979

74 653: US Pat Fulltext_1980-1989

571 654: US Pat.Full_1990-1998/Jul 28

4 763: Freedonia Market Res_1990-1998/Jul

2 764: BCC Market Research_1989-1998/Jun

50 files have one or more items; file list includes 145 files.

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Your last SELECT statement was:

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N1 571 654: US Pat.Full_1990-1998/Jul 28
N2 383 348: EUROPEAN PATENTS_1978-1998/Jul W3-
N3 138 5: BIOSIS PREVIEWS(R)_1969-1998/JUL W4
N4 116 155: MEDLINE(R)_1966-1998/Sep W4
N5 82 34: SciSearch(R) Cited Ref Sci_1990-1998/Jul W4
N6 74 653: US Pat.Fulltext_1980-1989
N7 69 73: EMBASE_1974-1998/Aug W1
N8 30 76: Life Sciences Collection_1982-1998/Jun
N9 30 94: JICST-EPlus_1985-1998/May W4
N10 25 377: Derwent Drug File_1983-1998/Jul W4

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N11	18	156: Toxline(R)_1965-1998/Jul
N12	18	331: DERWENT WPI_1963-1998/UD=9830;UP=9827;UM=9825
N13	17	144: Pascal 1973-1998/Jun
N14	16	16: IAC PROMT(R)_1972-1998/Aug 04
N15	13	652: US Patents Fulltext_1971-1979
N16	12	148: IAC Trade & Industry Database_1976-1998/Aug 04
N17	10	636: IAC Newsletter DB(TM)_1987-1998/Aug 04
N18	8	35: Dissertation Abstracts Online_1861-1998/Aug
N19	8	444: New England Journal of Med_1985-1998/Aug W1
N20	6	265: FEDRIP_1998/Jun

50 files have one or more items; file list includes 145 files.

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5	5:	BIOSIS PREVIEWS(R)_1969-1998/JUL W4
1	15:	ABI/INFORM(R)_1971-1998/Jul W4
2	16:	IAC PROMT(R)_1972-1998/Aug 04
2	34:	SciSearch(R) Cited Ref Sci_1990-1998/Jul W4
2	73:	EMBASE_1974-1998/Aug W1
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4	148:	IAC Trade & Industry Database_1976-1998/Aug 04
4	155:	MEDLINE(R)_1966-1998/Sep W4
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187	348:	EUROPEAN PATENTS_1978-1998/Jul W3-
1	377:	Derwent Drug File_1983-1998/Jul W4
2	444:	New England Journal of Med_1985-1998/Aug W1
2	457:	The Lancet_1986-1998/Jul W4
6	652:	US Patents Fulltext_1971-1979
32	653:	US Pat.Fulltext_1980-1989
310	654:	US Pat.Full_1990-1998/Jul 28
2	763:	Frederonia Market Res_1990-1998/Jul

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N1	310	654: US Pat.Full_1990-1998/Jul 28
N2	187	348: EUROPEAN PATENTS_1978-1998/Jul W3-
N3	32	653: US Pat.Fulltext_1980-1989
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N5	5	5: BIOSIS PREVIEWS(R)_1969-1998/JUL W4
N6	4	148: IAC Trade & Industry Database_1976-1998/Aug 04
N7	4	155: MEDLINE(R)_1966-1998/Sep W4
N8	2	16: IAC PROMT(R)_1972-1998/Aug 04
N9	2	34: SciSearch(R) Cited Ref Sci_1990-1998/Jul W4
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N17	0	6: NTIS_64-1998/Aug W5
N18	0	8: Ei Compendex(R)_1970-1998/Aug W4
N19	0	9: Business & Industry(R) Jul_1994-1998/Aug 04
N20	0	14: Mechanical Engineering Abs_1973-1998/Aug

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? b n5:m8,n10:n12:exs

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\$2.00 2.000 DialUnits File411
\$2.00 Estimated cost File411
\$2.00 Estimated cost this search
\$2.17 Estimated total session cost 2.053 DialUnits

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File 5:BIOSIS PREVIEWS(R) 1969-1998/JUL W4

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 File 73:EMBASE 1974-1998/Aug W1
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 File 444:New England Journal of Med. 1985-1998/Aug W1
 (c) 1998 Mass. Med. Soc.
 File 457:The Lancet 1986-1998/Jul W4
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Set Items Description

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File 357 Derwent Biotechnology Abs 1982-1998/Aug B2

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 595 VISCOSUS
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 DIALOG(R)File 357:Derwent Biotechnology Abs
 (c) 1998 Derwent Publ Ltd. All rts. reserv.
 141954 DBA Accession No.: 93-00006
 A procedure for large-scale plasmid isolation without using
 ultracentrifugation - plasmid DNA purification from Escherichia coli
 using alkaline extraction and precipitation
 AUTHOR: Chakrabarti A; Sitaric S; +Ohl S
 CORPORATE SOURCE: Center for Sickle Cell Disease, College of Medicine,
 Howard University, 2121 Georgia Ave. N.W., Washington, DC 20059, USA.
 JOURNAL: Biotechnol.Appl.Biochem. (16, 2, 211-15) 1992
 CODEN: BABIEC
 LANGUAGE: English
 ABSTRACT: An expedient procedure for large-scale plasmid isolation from
 Escherichia coli without using ultracentrifugation or special setups is
 described. Harvested cells are treated with lysozyme (EC-3.2.1.17) and
 then mixed with alkaline-SDS solution (0.2 M NaOH/1% SDS) to obtain a
 homogeneous viscous solution. Ammonium acetate is added to precipitate
 chromosomal DNA, which is then removed by centrifugation. The
 supernatant is filtered through Whatman No. 1 filter paper, and
 subjected to isopropanol precipitation and centrifugation. The pellet
 is resuspended in TE buffer and subjected to phenol and chloroform
 extractions and ethanol precipitation to remove contaminating DNA-ases.
 Finally, lithium chloride precipitation is performed to remove high
 mol.wt. RNAs, and the precipitated plasmid is collected by
 centrifugation. The method produces plasmid DNA in yields of about 2
 mg/l culture. The plasmids consist mostly of monomeric and dimeric
 covalently closed circular DNA. The plasmids can be digested with
 various restriction endonucleases and are compatible with gene cloning,
 transfection-gene expression and viral production. (8 ref)

3/7/11

DIALOG(R)File 357:Derwent Biotechnology Abs

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134059 DBA Accession No.: 92-06551

Cell harvesting using cross-flow microfiltration - cell recovery; review (conference paper)

AUTHOR: Howell J A; Lofkine M; Pritchard M

CORPORATE SOURCE: School of Chemical Engineering, University of Bath, Claverton Down, Bath, BA2 7AY, UK.

JOURNAL: NATO ASI Ser E (204, 237-52) 1991

CODEN: 9999X

LANGUAGE: English

ABSTRACT: Cell harvesting using cross-flow microfiltration is discussed with respect to: (1) terms and concepts (transmembrane pressure, cross-flow, flux, rejection coefficient, membrane resistance, cake resistance); (2) membranes; (3) modules; (4) operating modes; (5) operating factors (flux pressure, flux time, cross-flux flow velocity, temp, flux, viscosity); (6) cake deposits (backflushing, concentration, composition, charge); (6) theories (resistance in series, particle size and pore blockage, shear, lateral migration, shear-induced diffusion scour, retention and transmission and viability); and (7) application e.g. to yeast cell harvesting. Cross-flow microfiltration is used in cell harvesting to produce moderately concentrated cell pastes. Operating conditions including cross-flow velocity, transmembrane pressure, temp. and channel geometry influence the performance measured in terms of flux over time. Retention of macromolecules by the membrane due to fouling may increase during the operating period. The mechanism of mass transfer from the membrane surface is disputed, but thought by most to be shear-induced diffusion. (66 ref)

3/7/17

DIALOG(R)File 357:Derwent Biotechnology Abs

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107775 DBA Accession No.: 90-10466

Design and scaleup of an anchorage-dependent mammalian cell bioreactor - mammal cell culture vessel scale-up; use of Koch-Sulzer mixing elements as cell growth surfaces (conference paper)

AUTHOR: Paul Sr E L

CORPORATE AFFILIATE: Merck-USA

CORPORATE SOURCE: Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey 07065, USA.

JOURNAL: Ann N.Y.Acad.Sci (589, 642-49) 1990

CODEN: ANYVAA9

LANGUAGE: English

ABSTRACT: A culture vessel configuration that meets the requirements of growing anchorage-dependent mammalian cells and that is amenable to scale-up was developed. The design criteria were: uniform irrigation of

cell surfaces for nutrient supply, oxygen supply and pH regulation, low shear, high surface to volume ratio, surface compatibility with mammalian cells; ability to clean-in-place and sterilize-in-place; capability for scale-up; cell harvesting without enzyme treatment; and FDA approval. The system was based on the use of Koch-Sulzer static mixing elements as cell growth surfaces. These elements are made up of a series of baffles arranged to generate uniform blending as well as equal radial and axial flow distribution over a wide range of flow conditions from viscous to turbulent Reynold's numbers while operating at low fluid shear. The system was tested for growth of primary fowl embryo cells. Successful cell growth and measles virus infection and replication were achieved. 2 Methods of cell harvest were also investigated. The sterility record of the system was excellent. (3 ref)

3/7/19

DIALOG(R)File 357:Derwent Biotechnology Abs

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090645 DBA Accession No.: 89-08636

Harvesting and disruption of cells of recombinant E. coli in a continuous process for recombinant protein production, recovery and purification - (conference abstract)

AUTHOR: Robinson C W; +Glick B R; Sauer T; Wood D

CORPORATE SOURCE: Department of Biology, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1.

JOURNAL: Eur Congr Biotechnol. (Vol.2, 627) 1987

CODEN: 9999X

LANGUAGE: English

ABSTRACT: An integrated, multistage, continuous process for the production, recovery and purification of recombinant proteins was investigated. Biomass is produced in a 2-stage continuous loop fermentor, and following maximum gene expression, cells are continuously harvested by cross-flow microfiltration and subjected to disruption. The homogenizer effluent is then treated by either enzymatic (DNA-ase) or mechanical (ultrasonic) means in order to reduce viscosity and enhance the subsequent ultrafiltration step. The effects of microfiltration operating conditions (tangential shear rate, transmembrane pressure drop, cell concentration, membrane type, fermentation antifam) on the permeation flux and retentate cell concentration were examined for recombinant Escherichia coli cells producing phage T4 DNA-ligase. The effects of disruption conditions on percentage disruption and DNA-ligase release and the effect of viscosity reduction and other relevant ultrafiltration operating variables on the prefractionation recovery of active enzyme were also examined. Implications for recovery of other intracellular recombinant products were presented. (2 ref)

3/7/20

DIALOG(R)File 357:Derwent Biotechnology Abs

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090636 DBA Accession No.: 89-08627

Enzymatic treatment of fermentation broth in downstream processing
improvement of alkaline proteinase production - treatment with
alpha-amylase, beta-amylase, glucoamylase, cellulase, polyelectrolyte,
etc. (conference paper)

AUTHOR: Horvat T, Vrana M, Bosnjak M, Prestler B, Joveva S
CORPORATE SOURCE: PLIVA, Pharmaceutical, Chemical, Food and Cosmetic
Industry, Research Institute, 41000 Zagreb, Yugoslavia.
JOURNAL: Eur Congr Biotechnol. (Vol.2, 605-08) 1987
CODEN: 99999X

LANGUAGE: English

ABSTRACT: Enzyme treatment of harvested fermentation broth from cultivation
of *Bacillus* sp. BPA-101 on wheat meal was studied in an attempt to
improve downstream processing of alkaline protease production. The
effects of treatment with alpha-amylase (EC-3.2.1.2), beta-amylase
(EC-3.2.1.2), glucoamylase (EC-3.2.1.3) and cellulase (EC-3.2.1.4) on
broth filtration rate and filtrate properties (viscosity, dry matter
concentration and convenience for concentrating the product) were
studied. To elucidate the mechanism of enzymatic action as well as to
optimize the process, hydrolysis kinetics of fermentation broth
carbohydrates at different temp. was examined. Simultaneous treatment
of fermentation broth with cationic polyelectrolyte (10 g/l),
glucoamylase (900 AGU/l) and alpha-amylase (200 SKB U/l) gave the best
results. Increased temp. (25-45 deg) induced faster hydrolysis, but
treatment for 30 min at 35 deg was sufficient for efficient product
recovery. Experiments performed on pilot scale confirmed results
obtained on a laboratory scale. Filtration and ultrafiltration were
facilitated and products of better quality were obtained when enzyme
treatment was used. (3 ref)

3/7/21

DIALOG(R)File 357:Derwent Biotechnology Abs
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090600 DBA Accession No.: 89-08591

Studies on filtration resistance during cross-flow filtration of microbial
cell suspensions - *Escherichia coli* and *Saccharomyces cerevisiae*
(conference abstract)

AUTHOR: Riesmeier B, Kroner K H, Kula M R
CORPORATE AFFILIATE: Ges Biotechnol Forsch
CORPORATE SOURCE: Gesellschaft fuer Biotechnologische Forschung mbH,
Mascheroder Weg 1, D-3300 Braunschweig, Germany.
JOURNAL: Eur Congr Biotechnol. (Vol.2, 472) 1987
CODEN: 99999X

LANGUAGE: English

ABSTRACT: Cross-flow filtration is used for different solid-liquid
separations e.g. waste-water treatment. Microbial cell harvesting was

carried out with well defined *Escherichia coli* and *Saccharomyces*
cerevisiae fermentation broths. 2 Self-built laboratory scale module
types (tubes and a flat channel) were used, and the parameters
responsible for membrane fouling were studied in detail. Different
membrane materials, e.g. nylon and polypropylene, as well as different
pore sizes (0.1-1.2 µm) were used to investigate the structure of the
sub-layers formed. Variations of permeation rates were studied with
respect to the lengths of the channels. Layer heights decreased with
increasing channel length; layer heights between 0.5-30 µm were found.
The following parameters were responsible for fouling processes:
particle concentration and size, properties of the membrane material
(porosity, pore size), properties of the suspensions (viscosity,
antibium content), wall shear rate, compressibility of the suspended
particles, applied transmembrane pressure and the geometry of the
module system. (2 ref)

3/7/24

DIALOG(R)File 357:Derwent Biotechnology Abs
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086284 DBA Accession No.: 89-04275

Large-scale preparation of bacteriophage lambda by tangential flow
ultrafiltration for isolation of lambda DNA - for use in molecular
biology

AUTHOR: Renbhokar G W, +Khatri G S
CORPORATE SOURCE: Genetic Engineering Division, CSIR Centre for
Biochemicals, V.P. Chest Institute Building, Delhi-110007, India.
JOURNAL: Anal. Biochem. (176, 2, 373-74) 1989
CODEN: ANBCA2

LANGUAGE: English

ABSTRACT: A new method for large-scale phage lambda preparation from large
volumes of phage lysates is described. The method involves using
tangential flow ultrafiltration. *Escherichia coli* strain 1B3101
harboring phage lambda cts857indSam7 was grown in Luria broth in a
Chemap fermentor at 30 deg. The culture was heat shocked at 45 deg for
15 min and agitated for 3-5 hr at 37 deg. The cells were harvested
using a Pellicon HVL-P-000-C5 filter and diluted in buffer. This
concentration step was repeated and the concentrate was suspended in
buffer. Chloroform was added and the mixture was agitated. The increase
in viscosity of the lysate was due to the release of DNA. Crystalline
pancreatic DNA-ase-I and RNA-ase were added and the suspension was kept
at RT overnight. The supernatant was decanted to eliminate the settled
chloroform and centrifuged. The suspension was passed through Pellicon
HVL-P-000-C5 and PTHK-000-05 filters, subjected to Miniman concentration
cell treatment, and to a PTHK-OMPO4 membrane. The prepared phage DNA is
useful in molecular biology, both as a molecular marker and as a vector
for cloning large DNA fragments. (7 ref)

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04aug98 07:20:49 User208669 Session D1233.5
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\$0.00 34 Type(s) in Format 6
\$14.00 7 Type(s) in Format 7
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\$19.25 Estimated cost this search
\$19.65 Estimated total session cost 1.081 DialUnits
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